WEST

Help | Logout | Interrupt

Main Menu | Search Form | Posting Counts | Show S Numbers | Edit S Numbers | Preferences | Cases

Search Results -

Terms	Documents
(administ$8 and (UCP)) and protein and metabol$4 and (MHC or HLA)	9

Database: US Patents Full-Text Database; US Pre-Grant Publication Full-Text Database; JPO Abstracts Database; EPO Abstracts Database; Derwent World Patents Index; IBM Technical Disclosure Bulletins

Search: L8

Refine Search

Recall Text | Clear

Search History

DATE: Sunday, March 23, 2003 Printable Copy Create Case

Set Name side by side	Query	Hit Count	Set Name result set
	DB=USPT,PGPB,JPAB,EPAB,DWPI; PLUR=YES; OP=OR		
L8	(administ$8 and (UCP)) and protein and metabol$4 and (MHC or HLA)	9	L8
L7	(administ$8 and (UCP))and protein and metabol$4 and (MHC or HLA)	9	L7
L6	(administ$8 and (UCP))and protein and metabol$4	107	L6
L5	(administ$8 and (UCP))and protein	130	L5
L4	administ$8 and (UCP)	182	L4
L3	administ$8 near (UCP or (uncoupling adj protein))	2	L3
L2	administ$8 and (UCP or (uncoupling adj protein))	249	L2
L1	administ$4 near (UCP or (uncoupling adj protein))	0	L1

END OF SEARCH HISTORY

WEST Search History

DATE: Sunday, March 23, 2003

Set Name side by side	Query	Hit Count	Set Name result set
DB=USPT,PGPB,JPAB,EPAB,DWPI; PLUR=YES; OP=OR			
L5	cd4 near administ$4	31	L5
L4	(HLA adj dr) same ((fatty adj acid) or oleic)	10	L4
L3	oleic near administ?	0	L3
L2	L1 and (HLA adj dr)	1	L2
L1	(Newell) [in]	1225	L1

END OF SEARCH HISTORY

Connecting via Winsock to STN

Welcome to STN International! Enter x:x

LOGINID:ssspta1644axd

PASSWORD:
TERMINAL (ENTER 1, 2, 3, OR ?):2

* * * * * * * * * * Welcome to STN International * * * * * * * * * *

NEWS 1		Web Page URLs for STN Seminar Schedule - N. America
NEWS 2	Apr 08	"Ask CAS" for self-help around the clock
NEWS 3	Apr 09	BEILSTEIN: Reload and Implementation of a New Subject Area
NEWS 4	Apr 09	ZDB will be removed from STN
NEWS 5	Apr 19	US Patent Applications available in IFICDB, IFIPAT, and IFIUDB
NEWS 6	Apr 22	Records from IP.com available in CAPLUS, HCAPLUS, and ZCAPLUS
NEWS 7	Apr 22	BIOSIS Gene Names now available in TOXCENTER
NEWS 8	Apr 22	Federal Research in Progress (FEDRIP) now available
NEWS 9	Jun 03	New e-mail delivery for search results now available
NEWS 10	Jun 10	MEDLINE Reload
NEWS 11	Jun 10	PCTFULL has been reloaded
NEWS 12	Jul 02	FOREGE no longer contains STANDARDS file segment
NEWS 13	Jul 22	USAN to be reloaded July 28, 2002; saved answer sets no longer valid
NEWS 14	Jul 29	Enhanced polymer searching in REGISTRY
NEWS 15	Jul 30	NETFIRST to be removed from STN
NEWS 16	Aug 08	CANCERLIT reload
NEWS 17	Aug 08	PHARMAMarketLetter(PHARMAML) - new on STN
NEWS 18	Aug 08	NTIS has been reloaded and enhanced
NEWS 19	Aug 19	Aquatic Toxicity Information Retrieval (AQUIRE) now available on STN
NEWS 20	Aug 19	IFIPAT, IFICDB, and IFIUDB have been reloaded
NEWS 21	Aug 19	The MEDLINE file segment of TOXCENTER has been reloaded
NEWS 22	Aug 26	Sequence searching in REGISTRY enhanced
NEWS 23	Sep 03	JAPIO has been reloaded and enhanced
NEWS 24	Sep 16	Experimental properties added to the REGISTRY file
NEWS 25	Sep 16	CA Section Thesaurus available in CAPLUS and CA
NEWS 26	Oct 01	CASREACT Enriched with Reactions from 1907 to 1985
NEWS 27	Oct 21	EVENTLINE has been reloaded
NEWS 28	Oct 24	BEILSTEIN adds new search fields
NEWS 29	Oct 24	Nutraceuticals International (NUTRACEUT) now available on STN
NEWS 30	Oct 25	MEDLINE SDI run of October 8, 2002
NEWS 31	Nov 18	DKILIT has been renamed APOLLIT
NEWS 32	Nov 25	More calculated properties added to REGISTRY
NEWS 33	Dec 02	TIBKAT will be removed from STN
NEWS 34	Dec 04	CSA files on STN
NEWS 35	Dec 17	PCTFULL now covers WP/PCT Applications from 1978 to date
NEWS 36	Dec 17	TOXCENTER enhanced with additional content
NEWS 37	Dec 17	Adis Clinical Trials Insight now available on STN
NEWS 38	Dec 30	ISMEC no longer available
NEWS 39	Jan 13	Indexing added to some pre-1967 records in CA/CAPLUS
NEWS 40	Jan 21	NUTRACEUT offering one free connect hour in February 2003
NEWS 41	Jan 21	PHARMAML offering one free connect hour in February 2003
NEWS 42	Jan 29	Simultaneous left and right truncation added to COMPENDEX, ENERGY, INSPEC
NEWS 43	Feb 13	CANCERLIT is no longer being updated
NEWS 44	Feb 24	METADEX enhancements
NEWS 45	Feb 24	PCTGEN now available on STN
NEWS 46	Feb 24	TEMA now available on STN

```
NEWS 47  Feb 26  NTIS now allows simultaneous left and right truncation
NEWS 48  Feb 26  PCTFULL now contains images
NEWS 49  Mar 04  SDI PACKAGE for monthly delivery of multifile SDI results
NEWS 50  Mar 19  APOLLIT offering free connect time in April 2003
NEWS 51  Mar 20  EVENTLINE will be removed from STN

NEWS EXPRESS  January 6 CURRENT WINDOWS VERSION IS V6.01a,
              CURRENT MACINTOSH VERSION IS V6.0b(ENG) AND V6.0Jb(JP),
              AND CURRENT DISCOVER FILE IS DATED 01 OCTOBER 2002
NEWS HOURS    STN Operating Hours Plus Help Desk Availability
NEWS INTER    General Internet Information
NEWS LOGIN    Welcome Banner and News Items
NEWS PHONE    Direct Dial and Telecommunication Network Access to STN
NEWS WWW      CAS World Wide Web Site (general information)

Enter NEWS followed by the item number or name to see news on that
specific topic.

  All use of STN is subject to the provisions of the STN Customer
  agreement.  Please note that this agreement limits use to scientific
  research.  Use for software development or design or implementation
  of commercial gateways or other similar uses is prohibited and may
  result in loss of user privileges and other penalties.

  * * * * * * * * * * * * * STN  Columbus  * * * * * * * * * * * * * * *



FILE 'HOME' ENTERED AT 15:32:12 ON 23 MAR 2003

=>   file medline caplus embase biosis
COST IN U.S. DOLLARS                          SINCE FILE      TOTAL
                                                 ENTRY    SESSION
FULL ESTIMATED COST                               0.21       0.21

FILE 'MEDLINE' ENTERED AT 15:32:23 ON 23 MAR 2003

FILE 'CAPLUS' ENTERED AT 15:32:23 ON 23 MAR 2003
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
COPYRIGHT (C) 2003 AMERICAN CHEMICAL SOCIETY (ACS)

FILE 'EMBASE' ENTERED AT 15:32:23 ON 23 MAR 2003
COPYRIGHT (C) 2003 Elsevier Science B.V.  All rights reserved.

FILE 'BIOSIS' ENTERED AT 15:32:23 ON 23 MAR 2003
COPYRIGHT (C) 2003 BIOLOGICAL ABSTRACTS INC.(R)

=> s (fatty (1N) acid) (10N) (HLA (1N) DR)
L1            8 (FATTY (1N) ACID) (10N) (HLA (1N) DR)

=> dup rem l1
PROCESSING COMPLETED FOR L1
L2            5 DUP REM L1 (3 DUPLICATES REMOVED)

=> dis l2 1-5 ibib abs

L2   ANSWER 1 OF 5     MEDLINE                                  DUPLICATE 1
ACCESSION NUMBER:    2002162755      MEDLINE
DOCUMENT NUMBER:     21891781   PubMed ID: 11895158
TITLE:               Immunomodulation by perioperative administration of n-3
                     fatty acids.
AUTHOR:              Weiss G; Meyer F; Matthies B; Pross M; Koenig W; Lippert H
CORPORATE SOURCE:    Department of Surgery, University Hospital, Medical
```

Faculty, Otto von Guericke University, Magdeburg, Germany..
Guenter.Weiss@Medizin.Uni-Magdeburg.DE
SOURCE: BRITISH JOURNAL OF NUTRITION, (2002 Jan) 87 Suppl 1 S89-94.
Journal code: 0372547. ISSN: 0007-1145.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: (CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
(RANDOMIZED CONTROLLED TRIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200204
ENTRY DATE: Entered STN: 20020317
Last Updated on STN: 20020419
Entered Medline: 20020418

AB It has been increasingly reported that administration of n-3 fatty acids is beneficial in patients with inflammatory processes. This effect is most likely caused by different biological characteristics, including an immunomodulating effect of the products derived from n-3 fatty acids through eicosanoid metabolism. The aim of this study was to investigate the effect of perioperative administration of n-3 fatty acids on inflammatory and immune responses as well as on the postoperative course of patients with extended surgical interventions of the abdomen. In particular, the effect of n-3 **fatty acids** on interleukin-6 release and on granulocyte/monocyte function (**HLA-DR** expression) was studied. There was a downregulation of the inflammatory response, and, simultaneously, a smaller postoperative immune suppression in the n-3 fatty acid group. In addition, we observed shorter postoperative periods in the intensive care unit and on the regular medical wards as well as lower rates of severe infections. The results suggest that perioperative administration of n-3 fatty acids may have a favourable effect on outcome in patients with severe surgical interventions by lowering the magnitude of inflammatory response and by modulating the immune response.

L2 ANSWER 2 OF 5 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2000:55614 CAPLUS
DOCUMENT NUMBER: 132:193682
TITLE: n-3 Polyunsaturated fatty acids inhibit the antigen-presenting function of human monocytes
AUTHOR(S): Hughes, David A.; Pinder, Andrew C.
CORPORATE SOURCE: Diet, Health and Consumer Science Division, Institute of Food Research, Norwich Research Park, Norwich, NR4 7UA, UK
SOURCE: American Journal of Clinical Nutrition (2000), 71(1, Suppl.), 357S-360S
CODEN: AJCNAC; ISSN: 0002-9165
PUBLISHER: American Society for Clinical Nutrition
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Diets rich in n-3 polyunsatd. fatty acids (PUFA) are assocd. with suppression of cell-mediated immune responses. The n-3 PUFA may inhibit the function of human antigen-presenting cells. A prerequisite for this role of blood monocytes is the cell surface expression of major histocompatibility complex (MHC) class II mols. [human leukocyte antigen (HLA)-DR, -DP, and -DQ], aided by the presence of intercellular adhesion mol.-1 (ICAM-1) and leukocyte function assocd. antigens 1 and 3. Eicosapentaenoic acid (EPA, C20:5n-3) can inhibit the expression of HLA-DR on nonstimulated human monocytes in vitro, but docosahexaenoic acid (DHA, C22:6n-3) enhances its expression. Both n-3 PUFA suppress the expression of HLA-DR, HLA-DP, and ICAM-1 on interferon-.gamma.-activated monocytes. Dietary fish oil supplementation can inhibit the expression of these surface mols. on circulating human monocytes. When EPA and DHA were combined in the same ratio as in common fish oil supplement capsules (3:2), there was no significant effect in vitro on the expression of HLA-DR on unstimulated monocytes, but the expression on activated

monocytes remained inhibited. In the same in vitro system, the ability of activated monocytes to present antigen to autologous lymphocytes was decreased after culture with the combined n-3 PUFA. The findings suggest a mechanism for the beneficial effects of fish oil in the treatment of rheumatoid arthritis, a disorder assocd. with elevated expression of MHC class II and adhesion mols. on monocytes within affected joints.
REFERENCE COUNT: 21 THERE ARE 21 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 3 OF 5 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2000:595556 CAPLUS
DOCUMENT NUMBER: 134:16990
TITLE: Effects of parenteral lipid emulsions with different fatty acid composition on immune cell functions in vitro
AUTHOR(S): Granato, Dominique; Blum, Stephanie; Rossle, Claudia; Le Boucher, Jacques; Malnoe, Armand; Dutot, Guy
CORPORATE SOURCE: Nestle Research Center, Nestec LTD, Lausanne, Switz.
SOURCE: JPEN, Journal of Parenteral and Enteral Nutrition (2000), 24(2), 113-118
CODEN: JPENDU; ISSN: 0148-6071
PUBLISHER: American Society for Parenteral and EnteralNutrition
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Background: Numerous studies suggest that immune function may be compromised by lipid emulsions rich in polyunsatd. fatty acids (PUFAs). In our study, we compared the effect of a new olive oil-based lipid emulsion (ClinOleic) contg. a moderate level of PUFAs, with emulsions based on soybean oil (Intralipid or Ivelip), on immune functions of human cell in vitro. Methods: Peripheral white blood cells were collected from healthy volunteers. Lymphocyte proliferation was evaluated by [3H]-thymidine incorporation after stimulation with either phytohemagglutinin (PHA) or antibodies against T-cell specific antigens. Lymphocytes subsets and T-cell activation markers (CD25 and HLA-DR) were measured by flow cytometry. The release of cytokines (interleukin [IL]-2, IL-1.beta., and tumor necrosis factor- .alpha. [TNF-.alpha.]) was measured by ELISA (ELISA), after lymphocytes or monocytes/macrophages stimulation with PHA or lipopolysaccharide (LPS). Results: A significant dose-dependent inhibition of thymidine incorporation was obsd. with Intralipid and Ivelip (incorporation down to 39.9% of control, $p < .001$) whereas ClinOleic showed no inhibitory effect. Activation antigen expression on both CD4- and CD8+ T-cells tended to decrease with Intralipid (CD25: -53.4% on CD4+ and -57.4% on CD8+; HLA-DR: -61.5% on CD4+ and -58.5% on CD8+) but not with ClinOleic (from -2.9% for CD25 on CD4+ to 16.7% for HLA-DR on CD4+). Intralipid decreased significantly IL-2 prodn. (-39.0%, $p < .05$) whereas ClinOleic had little effect (-13.0%, NS). Intralipid and ClinOleic tended to inhibit to a similar extent the release of pro-inflammatory cytokines (TNF-.alpha.: -21.5% and -34.8%, IL-1.beta.: -45.1% and -40.3%; resp.). Conclusions: Our results suggest that an olive oil-based lipid emulsion could modulate immune response selectively, maintaining protective immunity and reducing inflammatory response. Olive oil may offer an immunol. neutral alternative to soybean oil for use in parenteral lipid emulsions.
REFERENCE COUNT: 39 THERE ARE 39 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 4 OF 5 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1998:182890 CAPLUS
DOCUMENT NUMBER: 128:269943
TITLE: Influence of arginine, omega-3 fatty acids and nucleotide-supplemented enteral support on systemic inflammatory response syndrome and multiple organ failure in patients after severe trauma
AUTHOR(S): Weimann, Arved; Bastian, Leonard; Bischoff, Werner E.; Grotz, Martin; Hansel, Matthias; Lotz, Joachim;

AUTHOR(S): Trautwein, Christian; Tusch, Gunter; Schlitt, Hans J.; Regel, Gerd
CORPORATE SOURCE: Klinik fur Abdominal- und Transplantationschirurgie, Medizinische Hochschule Hannover, Hannover, 30625, Germany
SOURCE: Nutrition (New York) (1998), 14(2), 165-172
CODEN: NUTRER; ISSN: 0899-9007
PUBLISHER: Elsevier Science Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The influence of an enteral diet supplemented with arginine, omega-3 fatty acids, and nucleotides (Impact, Sandoz, Switzerland) on the incidence of systemic inflammatory response syndrome (SIRS) and multiple organ failure (MOF) was studied in 32 patients after severe trauma. The patients with an injury severity score >20 were included in this prospective, randomized, double-blind, controlled study. Primary endpoints were the incidence of SIRS and MOF. Secondary endpoints were parameters of acute phase and immune response as well as infection rate, mortality, and hospital stay. In the test group, fewer SIRS days per patient were found during 28 d. MOF score was lower in the test group on d 3 and 8-11. Acute phase parameters showed lower C-reactive protein blood serum levels and fibrinogen blood plasma levels. HLA-DR expression on monocytes showed higher fluorescence activity on d 7. No difference was found for T-lymphocyte CD4/CD8 ratio, interleukin-2 receptor expression, infection rate, mortality (2/16 vs. 4/13), and hospital stay length. Thus, there are beneficial effects of arginine, omega-3 fatty acids, and nucleotide-supplemented enteral diet in critically ill patients.

L2 ANSWER 5 OF 5 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1997:811274 CAPLUS
DOCUMENT NUMBER: 128:114018
TITLE: n-3 polyunsaturated fatty acids modulate the expression of functionally associated molecules on human monocytes and inhibit antigen presentation in vitro
AUTHOR(S): Hughes, D. A.; Pinder, A. C.
CORPORATE SOURCE: Dep. Nutr. Diet Health, Norwich Lab., Norwich, NR4 7UA, UK
SOURCE: Clinical and Experimental Immunology (1997), 110(3), 516-523
CODEN: CEXIAL; ISSN: 0009-9104
PUBLISHER: Blackwell Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The n-3 polyunsatd. fatty acid (PUFA)-rich diets suppress cell-mediated immune responses, but the mechanisms are unclear. Specific immune responses are initiated by antigen-presenting cells (APC). Eicosapentaenoic acid (EPA, n-3 PUFA), inhibits in vitro the expression of HLA-DR antigen, an MHC class II mol. required for the normal APC function on human blood monocytes. Docosahexaenoic acid (DHA, n-3 PUFA) enhances the expression of this mol. on unstimulated monocytes, but both n-3 PUFA suppress its expression on interferon-.gamma. (IFN-.gamma.)-activated monocytes. When EPA and DHA were combined at the ratio commonly found in fish oil supplement capsules (3:2), there was no in vitro effect on the expression of HLA-DR on unstimulated monocytes, but the expression on IFN-.gamma.-activated monocytes remained inhibited. In the same in vitro system a significant redn. in the ability of IFN-.gamma.-activated monocytes to present tetanus toxoid antigen to autologous lymphocytes was obsd. following culture with the combined n-3 PUFA mix. Thus, n-3 PUFA may inhibit the antigen-presenting function of mononuclear phagocytes.

=> dis l2 1-5 kwic

L2 ANSWER 1 OF 5 MEDLINE DUPLICATE 1

AB . . . as on the postoperative course of patients with extended surgical interventions of the abdomen. In particular, the effect of n-3 **fatty acids** on interleukin-6 release and on granulocyte/monocyte function (**HLA-DR** expression) was studied. There was a downregulation of the inflammatory response, and, simultaneously, a smaller postoperative immune suppression in the. . .

L2 ANSWER 2 OF 5 CAPLUS COPYRIGHT 2003 ACS
IT Histocompatibility antigens
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(**HLA-DR**; dietary polyunsatd. n-3 **fatty acids** inhibit antigen-presenting function of human monocytes)

L2 ANSWER 3 OF 5 CAPLUS COPYRIGHT 2003 ACS
IT Histocompatibility antigens
RL: BOC (Biological occurrence); BSU (Biological study, unclassified); BIOL (Biological study); OCCU (Occurrence)
(**HLA-DR**; effects of parenteral lipid emulsions with different **fatty acid** compn. on immune cell functions in vitro)

L2 ANSWER 4 OF 5 CAPLUS COPYRIGHT 2003 ACS
IT Histocompatibility antigens
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(**HLA-DR**; arginine, omega-3 **fatty acids** and nucleotide-supplemented enteral nutrition in humans after severe trauma)

L2 ANSWER 5 OF 5 CAPLUS COPYRIGHT 2003 ACS
IT Histocompatibility antigens
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(**HLA-DR**; polyunsatd. n-3 **fatty acids** modulate expression of functionally assocd. mols. on human monocytes and inhibit antigen presentation in vitro)

=> s newell K?/au
L3 813 NEWELL K?/AU

=> s l3 and hla
L4 1 L3 AND HLA

=> dis l4 ibib abs

L4 ANSWER 1 OF 1 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 2000116931 EMBASE
TITLE: Absence of host B7 expression is sufficient for long-term murine vascularized heart allograft survival.
AUTHOR: Szot G.L.; Zhou P.; Sharpe A.H.; He G.; Kim O.; **Newell K.A.**; Bluestone J.A.; Thistlethwaite J.R. Jr.
CORPORATE SOURCE: G.L. Szot, Ben May Inst. for Cancer Research, Department of Surgery, University of Chicago, Chicago, IL 60637, United States
SOURCE: Transplantation, (15 Mar 2000) 69/5 (904-909).
Refs: 24
ISSN: 0041-1337 CODEN: TRPLAU
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 018 Cardiovascular Diseases and Cardiovascular Surgery
026 Immunology, Serology and Transplantation
037 Drug Literature Index
LANGUAGE: English

SUMMARY LANGUAGE: English
AB CD28 antagonists have been shown to promote long-term graft survival and induce donor-specific tolerance. In this study, the role of CD28/B7 costimulation and the relative importance of host versus donor B7 expression in allograft rejection was assessed in a murine abdominal vascularized heterotopic heart transplant model. Wild-type, CD28-deficient, or B7-1/B7-2- deficient C57BL/6 (B6) mice were grafted with allogeneic wild type or B7- 1/B7-2-deficient hearts. The results demonstrate allogeneic heart grafts survive long-term in mCTLA4Ig-treated B6 and untreated B7-1/B7-2-deficient B6 recipients but not CD28KO B6 mice. B7-1/B7-2KO B6 recipients treated with anti-CD28 (PV-1) or recombinant human IL-2 rejected the heart transplants indicating that these mice are immunologically competent to reject grafts if costimulatory signals are supplied or bypassed. Finally, there was no difference in rejection between normal animals transplanted with wild-type versus B7-1/B7-2-deficient hearts. These results support a critical role for B7-expressing host antigen presenting cells in the rejection of heart allografts in mice and differences among B7KO and CD28KO animals.

=> l3 and (HLA (1N) DR)
L3 IS NOT A RECOGNIZED COMMAND
The previous command name entered was not recognized by the system.
For a list of commands available to you in the current file, enter
"HELP COMMANDS" at an arrow prompt (=>).

=> s l3 and (HLA (1N) DR)
L5 0 L3 AND (HLA (1N) DR)

=> s l3 and CD4
L6 37 L3 AND CD4

=> dup rem l6
PROCESSING COMPLETED FOR L6
L7 16 DUP REM L6 (21 DUPLICATES REMOVED)

=> dis l7 1-16 ibib abs

L7 ANSWER 1 OF 16 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2003:126594 BIOSIS
DOCUMENT NUMBER: PREV200300126594
TITLE: A critical role for 4-1BB in allograft rejection mediated by CD8+ T cells.
AUTHOR(S): Kim, O. S. (1); Guo, Z.; Wang, J.; Hart, J.; Larsen, C. P.; **Newell, K. A.**
CORPORATE SOURCE: (1) University of Chicago, Chicago, IL, USA USA
SOURCE: Modern Pathology, (January 2003, 2003) Vol. 16, No. 1, pp. 124A. print.
Meeting Info.: 92nd Annual Meeting of the United States and Canadian Academy of Pathology Washington, D.C., USA March 22-28, 2003
ISSN: 0893-3952.
DOCUMENT TYPE: Conference
LANGUAGE: English

L7 ANSWER 2 OF 16 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2002:813948 CAPLUS
DOCUMENT NUMBER: 137:304769
TITLE: Use of a CD8+ T cell inhibitory agent in the presence of a **CD4**+ T cell inhibitory agent for inhibition of transplant rejection
INVENTOR(S): **Newell, Kenneth A.**; Fu, Yang-Xin
PATENT ASSIGNEE(S): University of Chicago, USA
SOURCE: PCT Int. Appl., 38 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002083162	A1	20021024	WO 2002-US11498	20020412

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2001-283821P P 20010413

AB The invention relates generally to the treatment, inhibition or prevention of immune-driven rejection of grafted tissue or cells in a recipient host. Compns. and methods disclosed herein capitalize on the discovery that treatment, inhibition or prevention of costimulation blockade-resistant rejection can be mediated by administering a pharmaceutically effective amt. of a CD8+ T cell inhibitory agent in the presence of a **CD4+** T cell inhibitory agent to a subject.

REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 3 OF 16 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2002:341393 BIOSIS
DOCUMENT NUMBER: PREV200200341393
TITLE: Membrane lymphotoxin regulates CD8+ T cell-mediated intestinal allograft rejection.
AUTHOR(S): Kim, O. S. (1); Guo, Z.; Wang, J.; Wu, Q. (1); Hart, J. (1); Fu, Y.-X. (1); **Newell, K. A.**
CORPORATE SOURCE: (1) University of Chicago, Chicago, IL USA
SOURCE: Laboratory Investigation, (January, 2002) Vol. 82, No. 1, pp. 133A. http://labinvest.uscapjournals.org/. print. Meeting Info.: Annual Meeting of the United States and Canadian Academy of Pathology Chicago, IL, USA February 23-March 01, 2002
ISSN: 0023-6837.
DOCUMENT TYPE: Conference
LANGUAGE: English

L7 ANSWER 4 OF 16 MEDLINE DUPLICATE 1
ACCESSION NUMBER: 2001567343 MEDLINE
DOCUMENT NUMBER: 21528906 PubMed ID: 11673481
TITLE: Cutting edge: membrane lymphotoxin regulates CD8(+) T cell-mediated intestinal allograft rejection.
AUTHOR: Guo Z; Wang J; Meng L; Wu Q; Kim O; Hart J; He G; Zhou P; Thistlethwaite J R Jr; Alegre M L; Fu Y X; **Newell K A**
CORPORATE SOURCE: Emory Transplant Center and Department of Surgery, Emory University School of Medicine, Atlanta, GA 30322, USA.
CONTRACT NUMBER: R01 HD73104 (NICHD)
R01 AI43579 (NIAID)
SOURCE: JOURNAL OF IMMUNOLOGY, (2001 Nov 1) 167 (9) 4796-800. Journal code: 2985117R. ISSN: 0022-1767.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200112

ENTRY DATE: Entered STN: 20011024
Last Updated on STN: 20020122
Entered Medline: 20011205

AB Blocking the CD28/B7 and/or CD154/CD40 costimulatory pathways promotes long-term allograft survival in many transplant models where **CD4** (+) T cells are necessary for rejection. When CD8(+) T cells are sufficient to mediate rejection, these approaches fail, resulting in costimulation blockade-resistant rejection. To address this problem we examined the role of lymphotoxin-related molecules in CD8(+) T cell-mediated rejection of murine intestinal allografts. Targeting membrane lymphotoxin by means of a fusion protein, mAb, or genetic mutation inhibited rejection of intestinal allografts by CD8(+) T cells. This effect was associated with decreased monokine induced by IFN-gamma (Mig) and secondary lymphoid chemokine (SLC) gene expression within allografts and spleens respectively. Blocking membrane lymphotoxin did not inhibit rejection mediated by **CD4**(+) T cells. Combining disruption of membrane lymphotoxin and treatment with CTLA4-Ig inhibited rejection in wild-type mice. These data demonstrate that membrane lymphotoxin is an important regulatory molecule for CD8(+) T cells mediating rejection and suggest a strategy to avoid costimulation blockade-resistant rejection.

L7 ANSWER 5 OF 16 MEDLINE DUPLICATE 2
ACCESSION NUMBER: 2001335335 MEDLINE
DOCUMENT NUMBER: 21295909 PubMed ID: 11403253
TITLE: CD8 T cell-mediated rejection of intestinal allografts is resistant to inhibition of the CD40/CD154 costimulatory pathway.
AUTHOR: Guo Z; Meng L; Kim O; Wang J; Hart J; He G; Alegre M L; Thistlethwaite J R Jr; Pearson T C; Larsen C P; **Newell K A**
CORPORATE SOURCE: Department of Surgery, University of Chicago, Illinois 60637, USA.
CONTRACT NUMBER: RO1 AI43579 (NIAID)
SOURCE: TRANSPLANTATION, (2001 May 15) 71 (9) 1351-4.
Journal code: 0132144. ISSN: 0041-1337.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200107
ENTRY DATE: Entered STN: 20010723
Last Updated on STN: 20010723
Entered Medline: 20010719

AB BACKGROUND: Disruption of the CD40/CD154 pathway inhibits rejection in numerous models. The importance of this pathway on intestinal allograft rejection was examined in this study. METHODS: Intestinal grafts from B6C3F1 mice transplanted into C57BL/6 recipients were assessed histologically for rejection. RESULTS: The monoclonal antibody to CD154, MR1, failed to inhibit rejection in wild-type mice. Similarly, CD154-/- recipient mice rejected intestinal allografts. MR1 did inhibit early rejection in CD8-/- mice, but had no effect in **CD4**-/- recipients. All MR1-treated CD8-/- recipients eventually developed rejection. No benefit was observed when blockade of the CD40/CD154 pathway by MR1 was combined with blockade of the CD28/B7 pathway by mCTLA4Ig. CONCLUSIONS: These data suggest that **CD4**+ T cells mediating intestinal allograft rejection may be more dependent upon the CD40/CD154 pathway than CD8+ T cells. This finding highlights the importance of identifying agents that suppress CD8+ T cell-mediated rejection.

L7 ANSWER 6 OF 16 MEDLINE DUPLICATE 3
ACCESSION NUMBER: 2001169302 MEDLINE
DOCUMENT NUMBER: 21168435 PubMed ID: 11266891
TITLE: Blockade of the CD40 pathway fails to prevent CD8 T cell-mediated intestinal allograft rejection.

AUTHOR: Meng L; Guo Z; Kim O; He G; Hart J; Szot G L; Wang J; Pearson T C; Larsen C P; **Newell K A**

CORPORATE SOURCE: Department of Surgery, The University of Chicago, Chicago, Illinois, USA.

CONTRACT NUMBER: AI43579 (NIAID)

SOURCE: TRANSPLANTATION PROCEEDINGS, (2001 Feb-Mar) 33 (1-2) 418-20.
Journal code: 0243532. ISSN: 0041-1345.

PUB. COUNTRY: United States

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 200106

ENTRY DATE: Entered STN: 20010702
Last Updated on STN: 20010702
Entered Medline: 20010628

L7 ANSWER 7 OF 16 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.

ACCESSION NUMBER: 2001:278684 BIOSIS

DOCUMENT NUMBER: PREV200100278684

TITLE: T cell subsets and CD28 signals in cardiac allograft rejection.

AUTHOR(S): Alegre, Maria-Luisa (1); Szot, Gregory; Zhou, Ping (1); Rulifson, Ingrid (1); Wang, Jun (1); Guo, Zhong (1); Kim, Oliver (1); **Newell, Kenneth (1)**; Thistlethwaite, J. Richard (1); Bluestone, Jeffrey

CORPORATE SOURCE: (1) The University of Chicago, 5841 S. Maryland Ave., MC 0930, Chicago, IL, 60637 USA

SOURCE: FASEB Journal, (March 7, 2001) Vol. 15, No. 4, pp. A350. print.
Meeting Info.: Annual Meeting of the Federation of American Societies for Experimental Biology on Experimental Biology 2001 Orlando, Florida, USA March 31-April 04, 2001
ISSN: 0892-6638.

DOCUMENT TYPE: Conference

LANGUAGE: English

SUMMARY LANGUAGE: English

AB Although blockade of CD28 costimulatory molecule in vivo results in long-term cardiac allograft survival in wildtype mice, CD28-deficient mice reject allografts. This study compared the mechanisms of allogeneic responses in vitro and in vivo in wildtype and CD28-deficient mice. In vitro, CFSE-MLR assays demonstrated that purified wildtype **CD4**+ T cells proliferated slightly better to irradiated allogeneic splenocytes than CD28-deficient **CD4**+ T cells. Furthermore, only wildtype but not CD28-deficient purified CD8+ T cells responded to alloantigen. However, the presence of either type of **CD4**+ T cells restored CD28-deficient CD8+ T cell proliferation to alloantigen. Proliferation of wildtype CD8+ T cells was absolutely dependent on either B7 or IL-2 signals, indicating that CD8+ T cells require either CD28 signals or the presence of **CD4**+ T cells to proliferate to alloantigen in vitro. In vivo, depletion of **CD4**+ T cells resulted in long-term cardiac allograft survival in both strains but depletion of CD8+ T cells prevented graft rejection only in CD28-deficient hosts. In addition, more CD8+ T cells were found infiltrating grafts from CD28-deficient mice, suggesting that CD8+ T cells play a more important role in cardiac allograft rejection in CD28-deficient hosts. In wildtype mice, cardiac allograft rejection was dependent on the presence of **CD4**+ T cells only in the initial phase of the alloresponse, as depletion of **CD4**+ T cells 4 days after transplantation did not prevent rejection which was then CD8-dependent. In contrast, depletion of **CD4**+ T cells in CD28-deficient mice on day 4 still prevented cardiac allograft rejection indicating longer requirements for **CD4**+ T cells in CD28-deficient mice. Taken together, these data suggest that both **CD4**+ and CD8+ T cells from CD28-deficient mice have impaired responses to alloantigen and need long-lasting cooperation to promote

heart rejection.

L7 ANSWER 8 OF 16 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2001:357436 BIOSIS
DOCUMENT NUMBER: PREV200100357436
TITLE: Transplantation and the CD28/CTLA4/B7 pathway.
AUTHOR(S): Alegre, M. (1); Fallarino, F.; Zhou, P.; Frauwirth, K.; Thistlethwaite, J.; **Newell, K.**; Gajewski, T.; Bluestone, J.
CORPORATE SOURCE: (1) University of Chicago, 5841 South Maryland Avenue, Room No 7N, Chicago, IL, 60637: malegre@midway.uchicago.edu USA
SOURCE: Transplantation Proceedings, (February March, 2001) Vol. 33, No. 1-2, pp. 209-211. print.
Meeting Info.: XVIII International Congress of the Transplantation Society Rome, Italy August 29-September 01, 2000 Transplantation Society
. ISSN: 0041-1345.
DOCUMENT TYPE: Conference
LANGUAGE: English
SUMMARY LANGUAGE: English

L7 ANSWER 9 OF 16 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:434603 CAPLUS
DOCUMENT NUMBER: 136:133433
TITLE: Different mechanisms of cardiac allograft rejection in wildtype and CD28-deficient mice
AUTHOR(S): Szot, Gregory L.; Zhou, Ping; Rulifson, Ingrid; Wang, Jun; Guo, Zhong; Kim, Oliver; **Newell, Kenneth A.**; Thistlethwaite, J. Richard; Bluestone, Jeffrey A.; Alegre, Maria-Luisa
CORPORATE SOURCE: Ben May Institute for Cancer Research, The University of Chicago, Chicago, IL, 60637, USA
SOURCE: American Journal of Transplantation (2001), 1(1), 38-46
CODEN: AJTMBR; ISSN: 1600-6135
PUBLISHER: Munksgaard International Publishers Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Although CD28 blockade results in long-term cardiac allograft survival in wildtype mice, CD28-deficient mice effectively reject heart allografts. This study compared the mechanisms of allogeneic responses in wildtype and CD28-deficient mice. Adoptive transfer of purified CD28-deficient T cells into transplanted nude mice resulted in graft rejection. However, this model demonstrated that the allogeneic T cell function was severely impaired when compared with wildtype T cells, despite similar survival kinetics. Cardiac allograft rejection depended on both **CD4**+ and CD8+ T cell subsets in CD28-deficient mice, whereas only **CD4**+ T cells were necessary in wildtype recipients. These results suggested that CD8+ T cells were more important in CD28-deficient than wildtype mice. In addn. to the CD8+ T cell requirement, allograft rejection in CD28-deficient mice was dependent on a sustained presence of **CD4**+ T cells, whereas it only required the initial presence of **CD4**+ T cells in wildtype mice. Taken together, these data suggest that **CD4**+ T cells from CD28-deficient mice have impaired responses to alloantigen in vivo, thus requiring long-lasting cooperation with CD8+ T cell responses to facilitate graft rejection. These results may help to explain the failure to promote graft tolerance in some preclin. and clin. settings.
REFERENCE COUNT: 42 THERE ARE 42 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

DUPLICATE 4

L7 ANSWER 10 OF 16 MEDLINE
ACCESSION NUMBER: 1999384046 MEDLINE
DOCUMENT NUMBER: 99384046 PubMed ID: 10452966
TITLE: Cutting edge: blockade of the CD28/B7 costimulatory pathway

inhibits intestinal allograft rejection mediated by **CD4**+ but not CD8+ T cells.

AUTHOR: **Newell K A**; He G; Guo Z; Kim O; Szot G L; Rulifson I; Zhou P; Hart J; Thistlethwaite J R; Bluestone J A

CORPORATE SOURCE: Department of Surgery, Committee on Immunology, Ben May Institute for Cancer Research, University of Chicago, IL 60637, USA.. newell@surgery.bsd.uchicago.edu

SOURCE: JOURNAL OF IMMUNOLOGY, (1999 Sep 1) 163 (5) 2358-62. Journal code: 2985117R. ISSN: 0022-1767.

PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals; AIDS
ENTRY MONTH: 199909
ENTRY DATE: Entered STN: 19990925
Last Updated on STN: 19990925
Entered Medline: 19990914

AB The effect of blocking the CD28/B7 costimulatory pathway on intestinal allograft rejection was examined in mice. Murine CTLA4Ig failed to prevent the rejection of allografts transplanted into wild-type or **CD4** knockout (KO) mice but did inhibit allograft rejection by CD8 KO recipients. This effect was associated with decreased intragraft mRNA for IFN-gamma and TNF-alpha and increased mRNA for IL-4 and IL-5. This altered pattern of cytokine production was not observed in allografts from murine CTLA4Ig-treated **CD4** KO mice. These data demonstrate that blockade of the CD28/B7 pathway has different effects on intestinal allograft rejection mediated by **CD4**+ and CD8+ T cells and suggest that these T cell subsets have different costimulatory requirements in vivo. The results also suggest that the inhibition of **CD4**+ T cell-mediated allograft rejection by CTLA4Ig may be related to down-regulation of Th1 cytokines and/or up-regulation of Th2 cytokines.

L7 ANSWER 11 OF 16 MEDLINE DUPLICATE 5
ACCESSION NUMBER: 1999118782 MEDLINE
DOCUMENT NUMBER: 99118782 PubMed ID: 9921809
TITLE: The role of CD8 and **CD4** T cells in intestinal allograft rejection: a comparison of monoclonal antibody-treated and knockout mice.

AUTHOR: He G; Hart J; Kim O S; Szot G L; Siegel C T; Thistlethwaite J R; **Newell K A**

CORPORATE SOURCE: Department of Surgery, University of Chicago, Illinois 60637, USA.

SOURCE: TRANSPLANTATION, (1999 Jan 15) 67 (1) 131-7. Journal code: 0132144. ISSN: 0041-1337.

PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; AIDS
ENTRY MONTH: 199902
ENTRY DATE: Entered STN: 19990311
Last Updated on STN: 19990311
Entered Medline: 19990222

AB BACKGROUND: The relative contribution of CD8 and **CD4** T cells to allograft rejection remains an unresolved issue. Experimental results suggest that the relative importance of these T-cell subsets may vary depending on the model used and the organ studied. We have previously shown that treatment of murine recipients of intestinal allografts with a depleting anti-CD8 or a depleting anti-**CD4** monoclonal antibody (mAb) significantly inhibited allograft rejection. This study was undertaken to further examine the contribution of CD8 and **CD4** T cells to the rejection of intestinal allografts. METHODS: Intestinal allografts from B6C3F1/J (C57BL/6 x C3H/HeJ) mice were transplanted into C57BL/6 recipients. Recipient groups included mice with an acquired deficiency in CD8 or **CD4** T cells caused by treatment with

depleting mAb or mice genetically deficient in CD8 or **CD4** T cells as a result of disruption of the genes encoding major histocompatibility complex (MHC) class I, MHC class II, CD8, or **CD4**. In all cases, rejection was assessed histologically at predetermined time points. In some recipient groups, graft function was also assessed using a maltose absorption assay. RESULTS: Rejection, assessed between days 10 and 28 after transplantation, was significantly inhibited in mice deficient in CD8 or **CD4** T cells after treatment with depleting mAb. In contrast, mice genetically deficient in either CD8 T cells (MHC class I or CD8 knockouts) or **CD4** T cells (MHC class II or **CD4** knockouts) rejected intestinal allografts promptly. Both histologic and functional evaluation of anti-CD8 mAb-treated mice on day 60 showed that the inhibition of rejection persisted even after the return of a substantial number of CD8 T cells. Although intestinal allografts from anti-CD8 mAb-treated mice displayed little to no evidence of rejection on day 60 after transplantation, these mice were able to reject both donor and third-party skin grafts. CONCLUSIONS: These results demonstrate that the inhibition of intestinal allograft rejection associated with mAb treatment is not attributable solely to depletion of CD8 or **CD4** T cells. Furthermore, anti-CD8 mAb administration did not induce donor-specific tolerance or cause nonspecific immune suppression, as indicated by the skin-grafting experiments. Our findings suggest that at least some depleting mAbs mediate their protective effect on allograft rejection via an alternative mechanism such as the induction of a regulatory cell population(s).

L7 ANSWER 12 OF 16 MEDLINE DUPLICATE 6
ACCESSION NUMBER: 1998418027 MEDLINE
DOCUMENT NUMBER: 98418027 PubMed ID: 9745505
TITLE: Role of CD8+ and **CD4**+ T cells in the rejection of murine intestinal allografts.
AUTHOR: He G; Hart J; Thistlethwaite J R Jr; **Newell K A**
CORPORATE SOURCE: Department of Surgery, University of Chicago, Pritzker School of Medicine, Illinois, USA.
SOURCE: TRANSPLANTATION PROCEEDINGS, (1998 Sep) 30 (6) 2592-3. Journal code: 0243532. ISSN: 0041-1345.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; AIDS
ENTRY MONTH: 199810
ENTRY DATE: Entered STN: 19981021
Last Updated on STN: 19981021
Entered Medline: 19981013

L7 ANSWER 13 OF 16 MEDLINE DUPLICATE 7
ACCESSION NUMBER: 1998018661 MEDLINE
DOCUMENT NUMBER: 98018661 PubMed ID: 9381541
TITLE: Treatment with either anti-**CD4** or anti-CD8 monoclonal antibodies blocks alphabeta T cell-mediated rejection of intestinal allografts in mice.
AUTHOR: **Newell K A**; He G; Hart J; Thistlethwaite J R Jr
CORPORATE SOURCE: Department of Surgery, University of Chicago, Illinois 60637, USA.
SOURCE: TRANSPLANTATION, (1997 Oct 15) 64 (7) 959-65. Journal code: 0132144. ISSN: 0041-1337.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199711
ENTRY DATE: Entered STN: 19971224
Last Updated on STN: 19971224
Entered Medline: 19971107
AB BACKGROUND: Rejection is the major barrier preventing the more widespread

application of intestinal transplantation as treatment for intestinal failure. For this study, a one-way host-versus-graft murine model was used to investigate the contribution of T cell subsets to the rejection of allogeneic intestinal allografts. METHODS: Intestinal grafts consisting of the donor jejunum and ileum were procured from C57BL/6J (syngeneic group) and B6C3F1/J (C57BL/6 x C3H/HeJ, allogeneic group) mice. These grafts were then transplanted into (1) normal, (2) antibody-treated, or (3) genetically mutated C57BL/6 mice. Mice were killed at predetermined intervals and the grafts assessed for rejection by a blinded pathologist. RESULTS: No syngeneic mice demonstrated any evidence of rejection. In contrast, the recipients of allografts experienced progressive rejection. Recipient mice treated with tacrolimus developed significantly less severe allograft rejection. None of the alphabeta T cell-deficient recipient mice (T cell receptor beta chain knockout mice) experienced allograft rejection with follow-up ranging from 8 to 28 days. However, mice deficient in gammadelta T cells (T cell receptor delta chain knockout mice) rejected intestinal allografts in a manner indistinguishable from normal recipients. In order to investigate the role of **CD4**+ and CD8+ T cells, recipient mice were treated 2 days before transplantation with depleting monoclonal antibodies specific for either **CD4**+ cells or CD8+ cells. Depletion of either population of cells significantly inhibited allograft rejection. CONCLUSIONS: These data demonstrate that rejection of intestinal allografts in the murine model was absolutely dependent on alphabeta but not gammadelta T cells. Furthermore, both **CD4**+ and CD8+ T cells were necessary for small bowel allograft rejection. Additional studies will be required to determine whether the effects of monoclonal antibody treatment were due solely to depletion of T cells or were mediated at least in part through an active process that altered the functional properties of the targeted T cell subset.

L7 ANSWER 14 OF 16 MEDLINE DUPLICATE 8

ACCESSION NUMBER: 94014428 MEDLINE
DOCUMENT NUMBER: 94014428 PubMed ID: 8409442
TITLE: Involvement of TCR-V beta 8.3+ cells in the cure of mice bearing a large MOPC-315 tumor by low dose melphalan.
AUTHOR: Mokyr M B; Rubin M; **Newell K A**; Prokhorova A; Bluestone J A
CORPORATE SOURCE: Department of Biochemistry, University of Illinois at Chicago 60680.
CONTRACT NUMBER: CA-01350 (NCI)
CA49260 (NCI)
CA54413 (NCI)
SOURCE: JOURNAL OF IMMUNOLOGY, (1993 Nov 1) 151 (9) 4838-46.
Journal code: 2985117R. ISSN: 0022-1767.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199311
ENTRY DATE: Entered STN: 19940117
Last Updated on STN: 19940117
Entered Medline: 19931117

AB We have previously shown that the curative efficacy of low dose melphalan (L-phenylalanine mustard; L-PAM) for mice bearing a large s.c. MOPC-315 tumor requires the participation of CD8+ (but not **CD4**+) T cell-dependent antitumor immunity. Here we show that CD8+ T cells obtained from regressing tumors on day 4 or 5 after low dose L-PAM therapy of MOPC-315 tumor bearers (L-PAM TuB mice) display a preferential enhancement in the utilization of the TCR-V beta 8.3 gene segment as compared to CD8+ T cells from normal lymph nodes. Treatment of L-PAM TuB mice with mAb F23.1, which leads to the depletion of V beta 8.3+ cells, as well as V beta 8.1 and 8.2+ cells, led to a significant reduction in the ability of their tumor-infiltrating lymphocytes as well as their spleen cells to lyse MOPC-315 tumor cells in vitro in a short term assay. In addition, the mAb F23.1 treatment almost completely abrogated the lytic activity of the

tumor-infiltrating lymphocytes against another syngeneic, antigenically related plasmacytoma (the MOPC-104E). Moreover, the mAb F23.1 treatment significantly reduced the curative effectiveness of low dose L-PAM for mice bearing a large MOPC-315 tumor. In contrast, mAb KJ16 treatment, which leads to the depletion of V beta 8.1 and 8.2+ cells (but not V beta 8.3+ cells), did not reduce significantly the curative effectiveness of low dose L-PAM for such MOPC-315 tumor bearers. Thus, V beta 8.3+ T cells are important for the curative effectiveness of low dose L-PAM therapy for MOPC-315 tumor bearers, and it is conceivable that the V beta 8.3+ cells mediate their effect (at least in part) by contributing to the acquisition of CTL activity against plasmacytoma-shared Ag.

L7 ANSWER 15 OF 16 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 92268565 EMBASE
DOCUMENT NUMBER: 1992268565
TITLE: Immunopotentiation of anti-viral and anti-tumor immune responses using anti-T cell receptor antibodies and mitogens.
AUTHOR: **Newell K.A.**; Ellenhorn J.D.I.; Hirsch R.; Bluestone J.A.
CORPORATE SOURCE: Division of Transplantation, Department of Surgery, University of Chicago Hospitals,Chicago, IL 60637, United States
SOURCE: Annals of the New York Academy of Sciences, (1991) 636/- (279-287).
ISSN: 0077-8923 CODEN: ANYAA
COUNTRY: United States
DOCUMENT TYPE: Journal; Conference Article
FILE SEGMENT: 004 Microbiology
016 Cancer
026 Immunology, Serology and Transplantation
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Although the immunosuppressive properties of anti-CD3 mAbs are now widely recognized, we have accumulated data characterizing the T cell activating properties of these antibodies. While in some situations these activating properties may be viewed as unwanted side-effects (for instance OKT3-mediated T cell activation may be responsible for some of the first dose toxicity seen with patients receiving OKT3 for suppression of allograft rejection), we have shown that anti-CD3 mAb therapy can augment host immune responses and provide protection against some tumors and viral infections. Importantly, this augmented response allows the development of long term, specific immunity. Because the immunosuppressive and activating properties of anti-CD3 mAbs are so closely overlapping, we have sought to identify other agents that are capable of activating T cell subsets selectively. We have found that SEB activates T cell subsets selectively in vivo and that this activation can be exploited to prevent the outgrowth of a malignant murine tumor. Studies currently in progress, including phenotypic and functional analysis of TILs and in vivo T cell subset depletions, should result in a more precise understanding of how SEB-induced T cell activation inhibits tumor growth.

L7 ANSWER 16 OF 16 MEDLINE DUPLICATE 9
ACCESSION NUMBER: 91363906 MEDLINE
DOCUMENT NUMBER: 91363906 PubMed ID: 1832322
TITLE: Functional consequences of **CD4**-TCR/CD3 interactions.
AUTHOR: Julius M; **Newell K**; Maroun C; Haughn L
CORPORATE SOURCE: Department of Microbiology and Immunology, McGill University, Montreal, Quebec, Canada.
SOURCE: SEMINARS IN IMMUNOLOGY, (1991 May) 3 (3) 161-6. Ref: 49
Journal code: 9009458. ISSN: 1044-5323.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

General Review; (REVIEW)
(REVIEW, ACADEMIC)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199110
ENTRY DATE: Entered STN: 19911103
Last Updated on STN: 19911103
Entered Medline: 19911016

AB The relative positions of **CD4** and of the T cell receptor complex for antigen (TCR/CD3) determine whether signalling through the antigen receptor results in T cell growth. The following discussion focusses on those central observations which demonstrate that **CD4** and the associated protein tyrosine kinase p56lck provide critical signals modulating the biological responses induced through the TCR/CD3 complex. Based on the available evidence, we suggest that antigen-mediated co-aggregation of **CD4**/Lck and TCR/CD3 is an obligate activation signal and that, in its absence, signalling through TCR alpha beta induces T cell death. The role of **CD4** in self-non-self discrimination would therefore be critical and would provide a mechanism for the maintenance of peripheral T cell tolerance to non-major histocompatibility complex-related self-antigens.

=> s administ? (1N) CD4
L8 157 ADMINIST? (1N) CD4

=> s l8 and PD<19980417
'19980417' NOT A VALID FIELD CODE
3 FILES SEARCHED...
L9 82 L8 AND PD<19980417

=> dup rem l9
PROCESSING COMPLETED FOR L9
L10 38 DUP REM L9 (44 DUPLICATES REMOVED)

=> dis l10 ibib abs 1-38

L10 ANSWER 1 OF 38 CAPLUS COPYRIGHT 2003 ACS DUPLICATE 1
ACCESSION NUMBER: 1998:313832 CAPLUS
DOCUMENT NUMBER: 129:49258
TITLE: Effect of L-carnitine on human immunodeficiency virus-1 infection-associated apoptosis: a pilot study
AUTHOR(S): Moretti, Sonia; Alesse, Edoardo; Di Marzio, Luisa; Zazzeroni, Francesca; Ruggeri, Barbara; Marcellini, Sonia; Famularo, Giuseppe; Steinberg, Seth M.; Boschini, Antonio; Cifone, M. Grazia; De Simone, Claudio
CORPORATE SOURCE: Department of Infectious Diseases, University La Sapienza, Rome, Italy
SOURCE: Blood (**1998**), 91(10), 3817-3824
CODEN: BLOOAW; ISSN: 0006-4971
PUBLISHER: W. B. Saunders Co.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The Fas/Fas ligand system is involved in uncontrolled apoptosis, which ultimately leads to the loss of T lymphocytes in human immunodeficiency virus (HIV)-infected individuals. The signal transduced by Fas receptor involves the activation of an acidic sphingomyelinase, sphingomyelin breakdown, and ceramide prodn. Our recent reports have shown that L-carnitine inhibits Fas-induced apoptosis and ceramide prodn. both in vitro and in vivo. The aim of this study was to study, in a preliminary fashion, the impact of long-term L-carnitine **administration** on **CD4** and CD8 abs. counts, rate, and apoptosis in HIV-1-infected subjects. The generation of cell-assocd. ceramide and HIV-1 viremia was also investigated. Eleven, asymptomatic, HIV-1-infected subjects, who

refused any antiretroviral treatment despite experiencing a progressive decline of CD4 counts, were treated with daily infusions of L-carnitine (6 g) for 4 mo. Immunol. and virol. measures and safety were monitored at the start of the treatment and then on days 15, 30, 90, and 150. L-carnitine therapy resulted in an increase of abs. CD4 counts, which was statistically significant on day 90 and 150 (P = .010 and P = .019, resp.). A pos., not significant trend was also obsd. even in the change in abs. counts of CD8 lymphocytes. L-carnitine therapy also led to a drop in the frequency of apoptotic CD4 and CD8 lymphocytes. This redn. occurred gradually, but changes in actual values between each time point and baseline were strongly significant (P = .001 at the end of the study compared with the baseline). A strong redn. (P = .001) in cell-assocd. ceramide levels was found at the end of the study. In general, HIV-1 viremia increased slightly. No toxicity related to L-carnitine therapy was obsd. and dose redns. were not necessary. In HIV-1-infected subjects, long-term infusions of L-carnitine produced substantial increases in the rate and abs. counts of CD4 and, to a lesser degree, of CD8 lymphocytes. This was paralleled by a reduced frequency of apoptotic cells of both subgroups and a decline in the levels of ceramide. No clin. relevant change of HIV-1 viremia was obsd.

REFERENCE COUNT: 40 THERE ARE 40 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 2 OF 38 CAPLUS COPYRIGHT 2003 ACS DUPLICATE 2

ACCESSION NUMBER: 1998:714146 CAPLUS
DOCUMENT NUMBER: 130:123754
TITLE: Administration of thymocytes derived from non-pregnant mice induces an endometrial receptive stage and leukemia inhibitory factor expression in the uterus
AUTHOR(S): Fujita, Kazuyuki; Nakayama, Takahiro; Takabatake, Keiko; Higuchi, Toshihiro; Fujita, Jun; Maeda, Michiyuki; Fujiwara, Hiroshi; Mori, Takahide
CORPORATE SOURCE: Department of Gynecology and Obsterics, Faculty of Medicine, Kyoto University, Kyoto, 606-8507, Japan
SOURCE: Human Reproduction (**1998**), 13(10), 2888-2894
CODEN: HUREEE; ISSN: 0268-1161
PUBLISHER: Oxford University Press
DOCUMENT TYPE: Journal
LANGUAGE: English

AB We have previously reported that i.v. administration of splenocytes prepd. from mice in the early stages of pregnancy promoted embryo implantation in pseudopregnant mice. Since a T-lymphocyte-rich, but not a monocyte-rich prepn. from splenocytes enhanced embryo implantation, similar effects of thymocytes from non-pregnant mice on implantation were examd. in this study. Thymocytes were prepd. from immature 21 day old ICR female mice and the supernatant of a thymocyte suspension (Th-sup) was used as the control. Thymocytes or Th-sup were injected into the caudal vein of recipient mice on pseudopregnancy day 2, and blastocysts were transferred into the endometrial lumen. The implantation rates per recipient were significantly higher in the thymocyte-treated group. ICR mice were then oophorectomized on pseudopregnancy day 3. After 3-day progesterone supplementation, blastocysts were transferred with i.v. injection of thymocytes or Th-sup. Under progesterone supplementation, successful implantations were obsd. in the thymocyte-treated group, but not in the Th-sup-treated group. Reverse transcriptase-polymerase chain reaction anal. revealed that mRNA expression of leukemia inhibitory factor in the uterus was induced by thymocyte administration, but not by Th-sup. Thymocytes were divided into two populations, CD4(+/-)CD8(-) group and CD4(-)CD8(+/-) group, by sepn. columns. On pseudopregnancy day 2, the sepd. thymocytes in each group or their supernatant were injected into the endometrial stroma of the recipient mice, and blastocysts were transferred into the endometrial lumen. The **administration** of **CD4** (+/-) CD8(-) lymphocytes significantly promoted implantation rates, but no effect was obsd. in the CD4(-) CD8(+/-) group. These findings showed that thymocytes, esp. CD4-pos. lymphocytes, facilitate embryo implantation,

probably by regulating endometrial differentiation.
REFERENCE COUNT: 37 THERE ARE 37 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 3 OF 38 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.DUPLICATE 3
ACCESSION NUMBER: 1999006249 EMBASE
TITLE: CD4+ T cells can induce airway hyperresponsiveness to allergen challenge in the Brown Norway rat.
AUTHOR: Mishima H.; Hojo M.; Watanabe A.; Hamid Q.A.; Martin J.G.
CORPORATE SOURCE: Dr. J.G. Martin, Meakins-Christie Laboratories, McGill University, 3626 St. Urbain Street, Montreal, Que. H2X 2P2, Canada
SOURCE: American Journal of Respiratory and Critical Care Medicine, (**1998**) 158/6 (1863-1870).
Refs: 44
ISSN: 1073-449X CODEN: AJCMED
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 015 Chest Diseases, Thoracic Surgery and Tuberculosis
024 Anesthesiology
026 Immunology, Serology and Transplantation
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Airway hyperresponsiveness to inhalational challenge with methacholine (MCh) develops by 32 h after allergen challenge of actively sensitized BN rats. To test the hypothesis that CD4+ T cells mediate allergen-induced hyperresponsiveness independent of IgE-mediated mechanisms, we **administered CD4+** T cells, CD8+ T cells, and a mixture of CD4+ and CD8+ T cells (total T cells) isolated from the cervical lymph nodes of rats sensitized with ovalbumin (OA) to naive BN rats that underwent aerosol challenge with either OA or bovine serum albumin (BSA) 2 d later. Responsiveness to MCh was measured 2 d before transfer of T cells and 32 h after challenge with OA or BSA. Airway responsiveness increased significantly in recipients of CD4+ T cells after OA challenge, but not in any other of the treatment groups. Analysis of bronchoalveolar lavage (BAL) cells for major basic protein expression by immunostaining showed eosinophilia in OA-challenged CD4+ and total T-cell recipients. Cells retrieved by bronchoalveolar lavage showed increased expression of IL-5 mRNA (in situ hybridization) in CD4+ T cell recipients after OA challenge compared with other groups. Interferon-.gamma. mRNA was expressed to the greatest extent in CD8+ recipients, but it was elevated in both OA- and BSA-challenged animals. We conclude that CD4+ T cells can induce airway hyperresponsiveness after inhalational challenge with allergen and this is associated with IL-5 production and eosinophilia. CD8+ T cells may have a negative regulatory effect on responsiveness, possibly mediated by interferon-.gamma..

L10 ANSWER 4 OF 38 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 1998193998 EMBASE
TITLE: Immunological effect of preoperative intratumor administration of OK- 432 for advanced gastric cancer.
AUTHOR: Tokura N.; Kobayashi K.; Nakazaki H.; Washizawa N.; Kase H.; Watanabe M.; Nagasawa Y.; Tsujita K.; Yanagita K.; Yoshio T.
CORPORATE SOURCE: Dr. N. Tokura, First Department of Surgery, Toho University School of Medicine, 6-11-1 Omori-Nishi, Ota-ku, Tokyo 143-0015, Japan
SOURCE: Biotherapy, (**1998**) 12/5 (894-896).
Refs: 2
ISSN: 0914-2223 CODEN: BITPE
COUNTRY: Japan
DOCUMENT TYPE: Journal; Conference Article
FILE SEGMENT: 016 Cancer
026 Immunology, Serology and Transplantation
037 Drug Literature Index

048 Gastroenterology
LANGUAGE: Japanese
SUMMARY LANGUAGE: English; Japanese
AB In order to evaluate the influence of preoperative intratumor administration of OK-432, we selected 25 cases with stage II and III advanced gastric cancer to investigate the histological ICAM-1 and HLA-DR expression of cancer cells, and measure the immunological parameters. ICAM-1 and HLA-DR expression and the soluble ICAM-1 level were higher after **administration**. The **CD4**+ CD45RA- cell ratio increased before the operation, and the CD11b+ CD8 bright+ cell ratio decreased after the operation. We conclude that preoperatively intratumor administration of OK-432 is useful to improve host immunity in patients with advanced gastric cancer.

L10 ANSWER 5 OF 38 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 1998238320 EMBASE
TITLE: The effect of preoperative intratumoral administration of OK-432 on stage II and III gastric cancer patients.
AUTHOR: Tokura N.
CORPORATE SOURCE: N. Tokura, 1st Department of Surgery, Toho University School of Medicine, Funabashi-shi, Japan
SOURCE: Journal of the Medical Society of Toho University, (**1998**) 45/3 (356-367).
Refs: 31
ISSN: 0040-8670 CODEN: TOIZAG
COUNTRY: Japan
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 009 Surgery
037 Drug Literature Index
048 Gastroenterology
LANGUAGE: Japanese
SUMMARY LANGUAGE: English; Japanese
AB In order to evaluate the effect of preoperative intratumor administration of OK-432, I investigated the expression of HLA-DR, ICAM-1 and TIL in gastric cancer cells by immunohistochemical and HE staining, and by determining soluble ICAM-1 and immunological parameters. I selected 75 patients with stage II and III gastric cancer. These 75 cases were divided into three groups: no treatment group (n=30), which served as control, the OK-432 i.t. group (n=25) and the OK-432 i.d. group (n=20). In the OK-432 i.t. group, HLA-DR and ICAM-1 expression and soluble ICAM-1 level were higher after **administration**. The **CD4** + CD45RA - cell ratio increased 2 weeks after surgery, the CD11b+CD8 bright+ cell ratio began to decrease 2 weeks after. I conclude that the preoperative intratumor administration of OK-432 improve host immunity in patients with stage II and III gastric cancer.

L10 ANSWER 6 OF 38 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 1998233833 EMBASE
TITLE: Kinetics of W3/25 anti-rat CD4 monoclonal antibody. Studies on optimal doses and time-related effects.
AUTHOR: Caballero F.; Pelegri C.; Castell M.; Franch; Castellote C.
CORPORATE SOURCE: C. Castellote, Unit of Physiology, Faculty of Pharmacy, University of Barcelona, Av. Joan XXIII s/n, 3a planta, 08028 Barcelona, Spain. cristina@farmacia.far.ub.es
SOURCE: Immunopharmacology, (**1998**) 39/2 (83-91).
Refs: 25
ISSN: 0162-3109 CODEN: IMMUDP
PUBLISHER IDENT.: S 0162-3109(98)00011-3
COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 026 Immunology, Serology and Transplantation
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Although anti-CD4 monoclonal antibodies (MoAb) have been proven successful in preventing or treating adjuvant arthritis, little is known about the duration of the effects of these MoAb and their pharmacokinetics. In this work, we report the effects of a mouse anti-rat CD4 MoAb, named W3/25, on peripheral blood lymphocytes from female Wistar rats. Animals received a single dose of W3/25, from 1 to 3 mg, and blood was sampled at different time points from 0 h to 15 days after MoAb administration. After erythrocyte lysis, samples were stained by indirect immunofluorescence and analyzed by flow cytometry. Pharmacokinetic data were studied by assessing plasma levels of mouse IgG1 by ELISA-sandwich. W3/25 produced the down-regulation of surface CD4 molecule as early as 20 min after its administration at doses of 2 and 3 mg. The same effect was seen 30 min after a dose of 1 mg. The recovery of lymphocytes with normal expression of CD4 also depended of the dose **administered**. Thus, **CD4** + lymphocytes were recovered at 48, 72 and 96 h in rats treated with 1, 2 or 3 mg of W3/25, respectively. Plasma levels of free antibody were detectable from 20 min to 72 h, 60 min to 48 h and 60 min to 24 h after administration of 3, 2 and 1 mg, respectively, of W3/25. The mouse IgG1 MoAb used in this study followed a two-compartment model and its behavior was linear. Copyright (C) 1998 Elsevier Science B.V.

L10 ANSWER 7 OF 38 CAPLUS COPYRIGHT 2003 ACS DUPLICATE 4
ACCESSION NUMBER: 1997:802832 CAPLUS
DOCUMENT NUMBER: 128:113896
TITLE: Effects of subcutaneous interleukin-2 therapy on CD4 subsets and in vitro cytokine production in HIV+ subjects
AUTHOR(S): De Paoli, Paolo; Zanussi, Stefania; Simonelli, Cecilia; Bortolin, Maria Teresa; D'Andrea, Monica; Crepaldi, Cinzia; Talamini, Renato; Comar, Manola; Giacca, Mauro; Tirelli, Umberto
CORPORATE SOURCE: Department of Microbiology, Immunology, and Virology, Centro di Riferimento Oncologico, IRCCS, Aviano, 33081, Italy
SOURCE: Journal of Clinical Investigation (**1997**), 100(11), 2737-2743
CODEN: JCINAO; ISSN: 0021-9738
PUBLISHER: Rockefeller University Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB HIV infection is characterized by the redn. of the CD4+, CD45RA+, CD26+, and CD28+ lymphocyte subsets and of the in vitro prodn. of IL-2, IL-4, and interferon-.gamma.; on the contrary, chemokine prodn. is usually increased. These abnormalities are only partially restored by antiretroviral chemotherapy. Therapy with interleukin-2 has been proposed to restore the functions of the immune system, but the mechanisms by which IL-2 exerts its activities are unknown. The aim of this study was to define the effects of rIL-2 **administration** on **CD4**+, CD45RA+, CD45R0+, and CD26+ lymphocytes and on the in vitro prodn. of IL-2, IL-4, IL-10, IFN-.gamma., RANTES, and sCD30 in HIV+ patients. Ten HIV+ patients with CD4 cell counts between 200 and 500 cells/mm3 were treated with six cycles of s.c. recombinant IL-2 administration, in combination with zidovudine and didanosine. This therapeutic regimen resulted in a remarkable increase in the no. of CD4+ cells and in the prolonged redn. of the levels of viremia. CD45R01 cells were expanded during the first cycle of therapy, while CD45RA+/CD26+ cells predominated after the third cycle. At this time, the in vitro prodn. of IL-2, IL-4, IFN-.gamma., and sCD30 were significantly upregulated. These results demonstrate that rIL-2 in HIV+ patients induces the reconstitution of the CD4/CD45RA lymphocytes subtype. This expanded cell population recovered the ability to produce in vitro IL-2, IL-4, and IFN-.gamma.. These effects may be beneficial to HIV+ patients by improving their immune response to microorganisms or vaccines.

L10 ANSWER 8 OF 38 CAPLUS COPYRIGHT 2003 ACS DUPLICATE 5

ACCESSION NUMBER: 1997:520652 CAPLUS
DOCUMENT NUMBER: 127:204198
TITLE: A humanized form of a CD4-specific monoclonal antibody exhibits decreased antigenicity and prolonged plasma half-life in rhesus monkeys while retaining its unique biological and antiviral properties
AUTHOR(S): Reimann, Keith A.; Lin, Wenyu; Bixler, Sarah; Browning, Beth; Ehrenfels, Barbara N.; Lucci, Jodie; Miatkowski, Konrad; Olson, Dian; Parish, Thomas H.; Rosa, Margaret D.; Oleson, Frederick B.; Hsu, Yen Ming; Padlan, Eduardo A.; Letvin, Norman L.; Burkly, Linda C.
CORPORATE SOURCE: Division of Viral Pathogenesis, Department of Medicine, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, 02215, USA
SOURCE: AIDS Research and Human Retroviruses (**1997**), 13(11), 933-943
CODEN: ARHRE7; ISSN: 0889-2229
PUBLISHER: Liebert
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Certain monoclonal antibodies (MAbs) directed against CD4 can efficiently block HIV-1 replication in vitro. To explore CD4-directed passive immunotherapy for prevention or treatment of AIDS virus infection, the authors previously examd. the biol. activity of a nondepleting CD4-specific murine MAb, mu5A8. This MAb, specific for domain 2 of CD4, blocks HIV-1 replication at a post-gp120-CD4 binding step. When administered to normal rhesus monkeys, all CD4+ target cells were coated with antibody, yet no cell clearance or measurable immunosuppression occurred. However, strong anti-mouse Ig responses rapidly developed in all monkeys. Here, the authors report a successfully humanized form of mu5A8 (hu5A8) that retains binding to both human and monkey CD4 and anti-AIDS virus activity. When administered i.v. to normal rhesus monkeys, hu5A8 bound to all target CD4+ cells without depletion and showed a longer plasma half-life than mu5A8. Nevertheless, an anti-hu5A8 response directed predominantly against V region determinants did eventually appear within 2-4 wk in most animals. However, when hu5A8 was administered to rhesus monkeys chronically infected with the simian immunodeficiency virus of macaques, anti-hu5A8 antibodies were not detected. Repeated administration of hu5A8 in these animals resulted in sustained plasma levels and CD4+ cell coating with humanized antibody for 6 wk. These studies demonstrate the feasibility of chronic **administration** of **CD4**-specific MAb as a potential means of treating or preventing HIV-1 infection.

L10 ANSWER 9 OF 38 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.DUPLICATE 6
ACCESSION NUMBER: 97114921 EMBASE
DOCUMENT NUMBER: 1997114921
TITLE: CD4 monoclonal antibody administration in atopic dermatitis.
AUTHOR: Robinet E.; Stamm C.; Nicolas J.-F.; Faure M.; Mercatello A.; Coronel B.; Wijdenes J.; Bienvenu J.; Revillard J.-P.; Claudy A.
CORPORATE SOURCE: Dr. J.P. Revillard, Hopital Edouard Herriot, Pav. P, 69437 Lyon Cedex 3, France
SOURCE: Journal of the American Academy of Dermatology, (**1997**) 36/4 (582-588).
Refs: 30
ISSN: 0190-9622 CODEN: JAADDB
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 006 Internal Medicine
013 Dermatology and Venereology
026 Immunology, Serology and Transplantation
037 Drug Literature Index

038 Adverse Reactions Titles

LANGUAGE: English
SUMMARY LANGUAGE: English
AB Background: Atopic dermatitis (AD) is a chronic inflammatory dermatosis that probably involves a dysregulated activation of helper T cells, type 2 (Th2 cells). Severe refractory AD can be controlled by cyclosporine treatment. Objective: We attempted to determine whether short-term CD4 monoclonal antibody (mAb) therapy could improve severe AD in adults. Methods: The CD4 mAb, B-F5, was infused over 2 days in three patients with severe refractory AD and, for control purposes, in two patients with severe psoriasis. Results: Administration of B-F5 was well tolerated, despite moderate first dose side effects. Clinical improvement was observed in two patients. In the third patient, a dramatic worsening occurred between 8 and 30 days after treatment, associated with an increased percentage of activated CD4+, CD25+, HLA-DR+, and CD45 RO+ cells and peripheral blood eosinophilia. The same **CD4** mAb **administered** to two patients with severe psoriasis induced marked clinical improvement of the lesions. Conclusion: Although CD4 mAb infusion may be potentially useful in the treatment of AD, the risk of aggravating the Th1/Th2 imbalance in AD should be considered in the design of future protocols.

L10 ANSWER 10 OF 38 CAPLUS COPYRIGHT 2003 ACS DUPLICATE 7
ACCESSION NUMBER: 1997:538501 CAPLUS
DOCUMENT NUMBER: 127:199767
TITLE: The induction of operational tolerance is not prevented by simultaneous administration of cyclosporin A
AUTHOR(S): Hamano, Kimikazu; Ito, Hiroshi; Bushell, Andrew; Wood, Kathryn J.; Esato, Kensuke
CORPORATE SOURCE: First Dep. Surgery, Sch. Med., Yamaguchi Univ., Yamaguchi, 755, Japan
SOURCE: Transplant International (**1997**), 10(4), 293-298
CODEN: TRINE5; ISSN: 0934-0874
PUBLISHER: Springer
DOCUMENT TYPE: Journal
LANGUAGE: English
AB In this study, the effect of combining anti-CD4 monoclonal antibody (mAb) and cyclosporin (CyA) therapy at the time of transplantation was examd. A mouse cardiac allograft model was used. Anti-**CD4** mAb **administered** perioperatively induces long-term survival. The addn. of a short course of CyA given s.c. in a regimen of either a high-dose treatment or a std. dose treatment to the anti-CD4 mAb treatment protocol did not have a detrimental effect on graft survival. Despite having no significant effect on graft survival, the addn. of CyA to the treatment protocol did result in a significant decrease in the level of IL-2 present in the hearts 7 days after transplantation. The decrease in IL-2 prodn. was directly related to the presence of CyA in vivo. When CyA treatment was continued throughout the period during which unresponsiveness to the graft is induced by anti-CD4 mAb therapy, 50% of the grafted hearts were rejected once the CyA was discontinued. In conclusion, the combined use of anti-CD4 mAb therapy and CyA did not have a neg. effect on graft survival in this model when the two agents were used concurrently at the time of transplantation.

L10 ANSWER 11 OF 38 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.DUPLICATE 8
ACCESSION NUMBER: 96290294 EMBASE
DOCUMENT NUMBER: 1996290294
TITLE: G-CSF stimulation of donor myelopoiesis prolongs survival of relapsed BCR-ABL-positive acute lymphoblastic leukemia after allogeneic marrow transplantation.
AUTHOR: Keil F.; Kalhs P.; Haas O.A.; Fritsch G.; Lechner K.; Mannhalter C.; Greinix H.T.
CORPORATE SOURCE: Department of Medicine I, Bone Marrow Transplantation Unit,

University of Vienna, Wahringer Gurtel 18-20,A-1090 Vienna, Austria

SOURCE: Bone Marrow Transplantation, (**1996**) 18/3 (655-657).
ISSN: 0268-3369 CODEN: BMTRE

COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 016 Cancer
025 Hematology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English

AB An allogeneic sex-mismatched BMT which was performed in a male patient with BCR-ABL-positive ALL in second hematological and central nervous system relapse resulted in a CR for 12 months. After BMT, the patient was closely monitored with reverse transcription (RT)-PCR. One month before a third relapse RT-PCR became positive. During relapse G-CSF was administered. It specifically stimulated the donor-derived myelopoiesis and led to the stabilization of the disease for 8 months. Fluorescence in situ hybridization analyses of individual cell populations revealed that during the whole course of G-CSF **administration** granulocytes, **CD4**+, CD8+ and CD34+/CD10- cells were of female (donor) origin and only the CD34+/CD10+ cells which represented the leukemic blasts, were of male (host) origin.

L10 ANSWER 12 OF 38 CAPLUS COPYRIGHT 2003 ACS DUPLICATE 9
ACCESSION NUMBER: 1996:408416 CAPLUS
DOCUMENT NUMBER: 125:84562
TITLE: T cell regulation in adult transplantation tolerance
AUTHOR(S): Davies, Joanna D.; Martin, Gilly; Phillips, Jenny; Marshall, Sara E.; Cobbold, Stephen P.; Waldmann, Herman
CORPORATE SOURCE: Dep. of Pathology, Cambridge Univ., Cambridge, UK
SOURCE: Journal of Immunology (**1996**), 157(2), 529-533
CODEN: JOIMA3; ISSN: 0022-1767
PUBLISHER: American Association of Immunologists
DOCUMENT TYPE: Journal
LANGUAGE: English

AB An encounter of the mature immune system with Ag usually leads to an immune response. If Ag is **administered** with **CD4**- and CD8-specific mAbs, the outcome of the response can be tolerance. This form of tolerance is peripheral, Ag specific, and maintained lifelong, and is assocd. with the suppression of nontolerant cells by CD4 cells of the tolerant host. Here we demonstrate that the degree of suppression is dependent on the no. of suppressor cells. A neutralizing anti-IL-4 Ab was partially able to inhibit suppression, indicating a role for IL-4 in the regulation of Th1 rejection responses.

L10 ANSWER 13 OF 38 CAPLUS COPYRIGHT 2003 ACS DUPLICATE 10
ACCESSION NUMBER: 1996:389895 CAPLUS
DOCUMENT NUMBER: 125:55833
TITLE: Anti-CD4 monoclonal antibodies suppress murine collagen-induced arthritis only at the time of primary immunization
AUTHOR(S): Williams, Richard O.; Whyte, Anthony
CORPORATE SOURCE: Dep. of Immunology, Babraham Inst., Cambridge, CB2 4AT, UK
SOURCE: Cellular Immunology (**1996**), 170(2), 291-295
CODEN: CLIMB8; ISSN: 0008-8749
PUBLISHER: Academic
DOCUMENT TYPE: Journal
LANGUAGE: English

AB We have examd. the ability of a mixt. of two anti-CD4 mAbs to protect against collagen-induced arthritis. Anti-**CD4** mAbs,

administered around the time of primary immunization with type II collagen in adjuvant, reduced the subsequent incidence of arthritis from 67 to 16% (P<0.01 by Fisher exact test). However, anti-CD4 treatment 3 wk after the primary immunization did not significantly affect the incidence of arthritis. This result extends earlier findings concerning the lack of efficacy of anti-CD4 treatment in established collagen-induced arthritis. Next, the ability of anti-CD4 treatment to induce tolerance to bovine type II collagen (and hence protect against arthritis) was evaluated using a regime known to be capable of inducing tolerance to human .gamma.-globulin. Anti-CD4 treatment completely failed to induce tolerance to type II collagen, as judged by levels of anti-collagen antibody, or protect against collagen-induced arthritis. These findings highlight the potential limitations of anti-CD4 mAb depleting treatment in immunotherapy.

L10 ANSWER 14 OF 38 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 96345909 EMBASE
DOCUMENT NUMBER: 1996345909
TITLE: A study to assess the immunogenicity, reactogenicity and safety of hepatitis A vaccine administered subcutaneously to patients with congenital coagulation disorders.
AUTHOR: Zuckerman J.N.; Moore S.; Smith J.; Tyrrell H.; Baxter A.; Lee C.A.
CORPORATE SOURCE: Acad. Unit Travel Medicine Vaccines, Royal Free Hospital School Medicine, Rowland Hill Street,London NW3 2PF, United Kingdom
SOURCE: Haemophilia, (**1996**) 2/4 (235-239).
ISSN: 1351-8216 CODEN: HAEMF4
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 004 Microbiology
026 Immunology, Serology and Transplantation
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English
AB The objective was to compare the immunogenicity, reactogenicity and safety of an inactivated hepatitis A vaccine administered subcutaneously to patients with congenital coagulation disorders. Subjects, 97 patients with congenital coagulation disorders (67 men aged > 16 and 30 children aged .ltoreq. 16 years), received hepatitis A vaccine administered at 1440 ELISA (enzyme linked immunosorbent assay) units (ELU) to the adult group and at 720 ELU to the child group at 0 and 6 months by the subcutaneous route. The vaccine was well tolerated, with the incidence of adverse events decreasing with subsequent administration of vaccine. Overall, 90% of subjects seroconverted 1 month after the booster (95% confidence interval 76-97%), with 100% seroconversion occurring in the child group compared with 85% in the adult group. There was a corresponding progressive rise in geometric mean titres in each group and no significant difference in the geometric mean titres was found between the two groups. Of the subjects, 29% were HIV positive, 3% of children compared with 40% of adults. A lower rate of seroconversion was observed in subjects with low **CD4** counts. **Administration** of two doses of an inactivated hepatitis A vaccine at 1440 ELU in adults and 720 ELU in children is safe and highly immunogenic when given by the subcutaneous route.

L10 ANSWER 15 OF 38 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 96085863 EMBASE
DOCUMENT NUMBER: 1996085863
TITLE: Clinical improvement of a patient with severe psoriasis following **CD4** antibody **administration** despite a blocking antibody-host response.
AUTHOR: Robinet E.; Stamm C.; Morel P.; Claudy A.; Nicolas J.-F.; Mercatello A.; Coronel B.; Wijdenes J.; Revillard J.P.

CORPORATE SOURCE: Laboratory of Immunology, INSERM U.80, UCBL, Hopital Edouard-Herriot,F-69437 Lyon Cedex 3, France
SOURCE: European Journal of Dermatology, (**1996**) 6/2 (141-146).
ISSN: 1167-1122 CODEN: EJDEE4
COUNTRY: France
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 013 Dermatology and Venereology
026 Immunology, Serology and Transplantation
029 Clinical Biochemistry
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English; French

AB The host antibody response is responsible for interference with the clinical effectiveness of therapeutic monoclonal antibodies (mAbs). The patient's immunity against therapeutic mAbs is usually monitored and the presence of human anti-mouse antibodies (HAMAs) is considered as a contraindication to further administration. We previously reported in a pilot study that administration of a murine CD4 mAb, B-F5, induced a rapid, clinical improvement in patients with severe psoriasis. In the present study, we report the case of a patient who received two additional short-term administrations (2 days) of B-F5. Despite the presence of blocking anti-B-F5 antibodies before the last course, B-F5 infusion was well-tolerated and resulted in clinical improvement. Thus, short-term **administration** of **CD4** mAb could be clinically effective despite the presence of HAMAs. This observation suggests that assays for blocking antibodies should be re-evaluated with respect to their clinical relevance.

L10 ANSWER 16 OF 38 CAPLUS COPYRIGHT 2003 ACS DUPLICATE 11
ACCESSION NUMBER: 1996:168203 CAPLUS
DOCUMENT NUMBER: 124:258383
TITLE: Anti-CD4 monoclonal antibody reduces the dose of cyclophosphamide required to induce tolerance to H-2 haplotype identical skin allografts in mice
AUTHOR(S): Omoto, Kazuya; Nishimura, Yousuke; Nomoto, Kenichi; Kong, Young-Yun; Umesue, Masayoshi; Murakami, Yoshiyuki; Tomita, Yukihiro; Nomoto, Kikuo
CORPORATE SOURCE: Medical Institute of Bioregulation, Kyushu University, Fukuoka, Japan
SOURCE: Immunobiology (Stuttgart) (**1996**), 195(1), 16-32
CODEN: IMMND4; ISSN: 0171-2985
PUBLISHER: Fischer
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Cyclophosphamide (CP)-induced tolerance which consists of a single i.p. injection of 200 mg/kg CP 2 days after priming with 1.times.108 donor spleen cells (SC), leads to long-lasting donor-specific skin allograft tolerance in H-2 compatible, multi-minor antigen incompatible, murine strain combinations. In this system, the optimal dose of CP has been suggested to be 200 mg/kg, however, such a dose of CP causes strong myelosuppression. Here, the authors therefore attempted to reduce the dose of CP by **administering** anti-**CD4** monoclonal antibody (mAb) before donor cell priming in this tolerance-inducing system. When C3H/He (C3H; H-2k, Mls-1b) mice were injected i.p. with 200 .mu.g anti-CD4 mAb on day -3, 1.times.108 AKR/J (AKR; H-2k, Mls-1a) SC plus 3.times.107 bone marrow cells (BMC) i.v. on day -2 and then 100 mg/kg CP i.p. on day 0, a long-lasting donor-specific skin allograft tolerance was established; furthermore, the decreases in the no. of leukocytes and the concn. of Hb in the peripheral blood were all less in the C3H mice treated with this new combined protocol than in the C3H mice injected with 200 mg/kg CP following the previous protocol. In the periphery of these tolerant mice, the no. of donor-reactive V.beta.6+CD4+ T cells decreased and mixed chimerism was obsd. on both days 14 and 80. In the mice

injected with AKR SC, BMC plus 100 mg/kg CP without anti-CD4 mAb, the no. of V.beta.6+CD4+ T cells decreased on day 14, and then recovered by day 80 when the mixed chimerism disappeared. These results therefore suggest that the combined use of anti-CD4 mAb can reduce the dose of CP without affecting the efficiency of inducing donor-specific tolerance, probably due to the enhancement of the destruction effect of donor-reactive T cells by CP.

L10 ANSWER 17 OF 38 CAPLUS COPYRIGHT 2003 ACS DUPLICATE 12
ACCESSION NUMBER: 1995:794179 CAPLUS
DOCUMENT NUMBER: 123:196268
TITLE: Induction of antigen-specific T and B cell immunity in colon carcinoma patients by anti-idiotypic antibody
AUTHOR(S): Somasundaram, Rajasekharan; Zaloudik, Jan; Jacob, Lutz; Benden, Andrea; Sperlagh, Melinda; Hart, Ellen; Marks, Gerald; Kane, Michael; Mastrangelo, Michael; Herlyn, Dorothee
CORPORATE SOURCE: Wistar Institute, Philadelphia, PA, 19104, USA
SOURCE: Journal of Immunology (**1995**), 155(6), 3253-61
CODEN: JOIMA3; ISSN: 0022-1767
PUBLISHER: American Association of Immunologists
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Polyclonal goat anti-idiotypic Abs directed against anti-human gastrointestinal carcinoma mAb GA733 were administered to colon cancer patients who had their primary tumor and lymph node metastases removed before immunotherapy. Patients received 4 s.c. doses (0.5-8 mg each) of alum-pptd. anti-idiotypic Ab. Seven of the 13 patients produced anti-anti-Ids that bound specifically to the GA733 epitope on tumor cells and shared idiotopes with mAb GA733. In 4 of the 7 responding patients, anti-Id therapy specifically modulated T cell responses. In 2 patients who did not demonstrate GA733 antigen (Ag)/anti-Id-reactive T cells before therapy, anti-Id **administration** induced **CD4+**, MHC class II-dependent T cells that specifically proliferated in culture in response to stimulation with either anti-Id or GA733 Ag. In 2 other patients who did demonstrate Ag/anti-Id-reactive T cells before therapy, anti-Id administration transiently induced lymphocytes that suppressed the proliferative responses of cultured pretherapy lymphocytes to stimulation with anti-Id or GA733 Ag. Nine of the 13 treated patients showed no evidence of disease after 39-86 mo of observation. Five of these patients developed Ag-specific Ab3 and one had, in addn., a T cell response.

L10 ANSWER 18 OF 38 CAPLUS COPYRIGHT 2003 ACS DUPLICATE 13
ACCESSION NUMBER: 1995:897852 CAPLUS
DOCUMENT NUMBER: 123:312136
TITLE: Efficient replication of human immunodeficiency virus type 1 and measles virus in a human-to-mouse graft versus host disease model permits immunization research
AUTHOR(S): Huppes, Wim; Tenner-Racz, Klara; Kraal, Georg
CORPORATE SOURCE: Health Research-TNO, Rijswijk, 2280 HV, Neth.
SOURCE: Journal of General Virology (**1995**), 76(11), 2707-15
CODEN: JGVIAY; ISSN: 0022-1317
PUBLISHER: Society for General Microbiology
DOCUMENT TYPE: Journal
LANGUAGE: English
AB An acute graft vs. host disease (GvHD) murine model was developed to study the pathogenic and protective mechanisms against viruses that replicate in cells of the human immune system. The model allowed efficient replication of lymphotropic, macrophage and amphitropic strains of human immunodeficiency virus type 1 (HIV-1) and measles virus (MV). Cytopathic lymphotropic strains of HIV-1 and a wild-type MV strain replicated in a burst-like manner, whereas a non-cytopathic lymphotropic HIV-1 strain and

all macrophage-tropic HIV-1 strains caused persistent infection of the graft. The replication kinetics of infection with these viruses were highly reproducible and were very similar to those obsd. in natural infection of humans. Infection with these viruses, with the exception of HIV-1SF2, led to a significant delay and abrogation of the GvHD, indicating a direct immunosuppressive effect. Interestingly, infection with the lymphotropic HIV-1SF2 strain was rapidly and spontaneously abrogated. The model was also shown to be suitable for the evaluation of passive immunization strategies. Administration of a combination of antibodies against the HIV-1 V3 loop and the HIV-1 CD4 binding sites prevented subsequent infection with HIV-1IIIB. In contrast, **administration** of **CD4** binding site specific human monoclonal antibody at a concn. that would neutralize the virus in vitro enhanced in vivo infection with HIV-1IIIB. The model also allowed evaluation of in vivo immunization studies. Immunization with a live attenuated measles vaccine resulted in protection from a wild-type MV challenge, whereas immunization with a subunit candidate vaccine appeared to give partial protection.

L10 ANSWER 19 OF 38 CAPLUS COPYRIGHT 2003 ACS DUPLICATE 14
ACCESSION NUMBER: 1995:380001 CAPLUS
DOCUMENT NUMBER: 122:158563
TITLE: Intragraft expression of cytokine transcripts during pig proislet xenograft rejection and tolerance in mice
AUTHOR(S): Morris, Carolyne F.; Simeonovic, Charmaine J.; Fung, Ming-Chiu; Wilson, J. Dennis; Hapel, Andrew J.
CORPORATE SOURCE: The John Curtin School Med. Research, The Australian National University, Canberra, Australia
SOURCE: Journal of Immunology (**1995**), 154(5), 2470-82
CODEN: JOIMA3; ISSN: 0022-1767
PUBLISHER: American Association of Immunologists
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The rejection of pig proislet (islet precursor) xenografts in CBA/H mice is a CD4+ T cell-dependent process. The mol. mechanisms of xenograft rejection, xenograft survival during anti-CD4 mAb therapy, and xenograft tolerance post-withdrawal of anti-**CD4** mAb **administration** , were examd. by using a semiquant. PCR method. Temporal anal. of intragraft cytokine mRNA demonstrated a Th0-like pattern of expression (IL-2, IFN-.gamma., IL-3, IL-4, IL-5, and IL-10) on day 4 of the acute xenograft rejection process. From day 5, however, only Th2-assocd. transcripts (IL-3, IL-4, IL-5, and IL-10) were enhanced in xenografts compared with isograft controls. Immunohistochem. showed that the principal participants in the rejection infiltrate were CD4+ T cells and eosinophils, with smaller nos. of CD8+ T cells. In vivo depletion of CD4+ T cells prevented xenograft rejection but had minimal effect on the peak levels of IL-2, IFN-.gamma., and IL-10 mRNA; in contrast, the enhanced expression of IL-3, IL-4, and IL-5 transcripts seen in rejecting xenografts was abrogated. This established a pos. correlation between acute xenograft rejection, presence of CD4+ T cells, and enhanced intragraft expression of mRNA for the Th2-type cytokines IL-3, IL-4, and IL-5. In tolerant hosts, long-term proislet xenograft survival and function (>190 days) was accompanied by intragraft expression of IL-2 and IL-10 mRNA; IFN-.gamma., IL-3, IL-4, and IL-5 mRNA were either undetected or not enhanced. The induced rejection of long-term functioning xenografts (>170 days) in nontolerant hosts resulted in selective enhancement of IL-4 transcript expression. Thus, Th2-like CD4+ T cells are differentially activated in response to xenoantigen and xenograft tolerance is assocd. with lack of expression of the Th2 cytokine, IL-4.

L10 ANSWER 20 OF 38 CAPLUS COPYRIGHT 2003 ACS DUPLICATE 15
ACCESSION NUMBER: 1995:669324 CAPLUS
DOCUMENT NUMBER: 123:167125
TITLE: In vivo **administration** of **CD4**

-specific monoclonal antibody: Effect on provirus load in rhesus monkeys chronically infected with the simian immunodeficiency virus of macaques

AUTHOR(S): Reimann, Keith A.; Cate, Richard L.; Wu, Yaming; Palmer, Louise; Olson, Dian; Waite, Barry C. D.; Letvin, Norman L.; Burkly, Linda C.

CORPORATE SOURCE: Harvard Medical School, Beth Israel Hospital, Boston, MA, 02215, USA

SOURCE: AIDS Research and Human Retroviruses (**1995**), 11(4), 517-25
CODEN: ARHRE7; ISSN: 0889-2229

PUBLISHER: Liebert
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Since monoclonal antibodies (MAb) specific for CD4 are potent inhibitors of HIV and SIV replication in vitro, we explored their potential usefulness in vivo as an AIDS therapy. The anti-CD4 MAb 5A8 binds to domain 2 of the CD4 mol. and inhibits virus replication and virus-induced cell fusion at a postvirus binding step. Administration of this MAb to normal rhesus monkeys coats all circulating and lymph node CD4 cells and induces neither CD4 cell clearance nor measurable immunosuppression. In the present study, monkeys chronically infected with the simian immunodeficiency virus of macaques (SIVmac) had stable levels of SIVmac provirus in PBMC prior to treatment as measured by a quant. polymerase chain reaction technique. Six infected monkeys treated with anti-CD4 MAb demonstrated a significant decrease in SIVmac provirus level after 9 days. Of these monkeys, 3 had > 800 CD4 cells/.mu.l and developed strong antimouse Ig responses that prevented further treatment. The remaining 3 monkeys had < 800 CD4 cell/.mu.L and failed to develop anti-mouse Ig antibody responses. When treatment was continued for 12-21 days in these monkeys, a sustained or further decrease in SIVmac provirus load occurred over the extended treatment period. Four monkeys that received a control MAb of irrelevant specificity for 9-22 days showed either no significant change or a transient increase in SIVmac provirus. Thus, the passive administration of anti-CD4 MAb may exert a specific antiviral effect in controlling immunodeficiency virus infection in vivo.

L10 ANSWER 21 OF 38 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.DUPLICATE 16
ACCESSION NUMBER: 96036316 EMBASE
DOCUMENT NUMBER: 1996036316
TITLE: Apoptosis (PCD) of murine thymocytes induced by anti-CD4 McAb in vivo.

AUTHOR: Zhou H.; Duan D.; Yin Y.
CORPORATE SOURCE: Department of Immunology, Beijing Medical University,Beijing 100083, China

SOURCE: Chinese Journal of Microbiology and Immunology, (**1995**) 15/6 (376-381).
ISSN: 0254-5101 CODEN: ZWMZDP

COUNTRY: China
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 026 Immunology, Serology and Transplantation
037 Drug Literature Index

LANGUAGE: Chinese
SUMMARY LANGUAGE: Chinese; English

AB In previous experiments, we found that anti-**CD4** McAb **administration** led to depletion of thymocytes in mice. Here, we explored the possibility that anti-Cd4 McAb could induce apoptosis of thymocytes. It has been shown that cortical thymocytes underwent apoptosis as characterized by morphologic changes with chromatin condensation and DNA fragmentation after anti-CD4 injection in mice. A flow cytometric method for measuring the percentage of apoptotic nuclei (hypodiploid DNA) after PI staining, and colorimetric methods measure DNA fragmentation in the nuclear extracts, both of them were much higher in anti-CD4 group than thymocytes of normal mice, ($P < 0.01$ and $P < 0.001$). Anti-CD4 induced apoptosis was inhibited by cycloheximide or IL-2. The ladder pattern of

DNA fragments, characteristics of apoptosis, appeared in anti-CD4 group. All results indicated that the anti-CD4 McAb could accelerate apoptosis of thymocytes, therefore the number of thymocytes was decreased.

L10 ANSWER 22 OF 38 CAPLUS COPYRIGHT 2003 ACS DUPLICATE 17
ACCESSION NUMBER: 1995:473937 CAPLUS
DOCUMENT NUMBER: 122:237211
TITLE: T cell antigen receptor engagement abrogates CD4-mediated T cell deletion in vivo
AUTHOR(S): Wang, Zhi-qin; Dudhane, Anita; Orlikowsky, Thorsten; Hoffmann, Michael K.
CORPORATE SOURCE: Department Microbiology and Immunology, New York Medical College, Valhalla, NY, 10595, USA
SOURCE: International Immunology (**1995**), 7(2), 207-11
CODEN: INIMEN; ISSN: 0953-8178
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The authors have previously shown that the engagement of CD4 by specific antibody in the mouse initiates a T cell apoptosis response with the following features: spleen and lymph node CD4+ T cells migrate into the bloodstream within minutes of anti-**CD4 administration** where they exhibit the phenotype of null cells. If they are capable of expressing functional Fas protein on their surface they degrade their DNA and disintegrate rapidly. The authors show here that the engagement of the T cell antigen receptor blocks the CD4-mediated deletion process in mouse. Anti-CD4-reactive T cells avoid the exodus into the bloodstream when their TCR is engaged by anti-CD3 or by a superantigen, do not modulate surface receptors and are not deleted. In contrast to the apoptosis-inducing CD4-specific antibody which causes migration of lymphocytes from lymphoid organs into the blood stream, the T cell-activating CD3-specific antibody causes lymphoid cell redistribution in the opposite direction, from the bloodstream to lymphoid organs. The TCR-mediated protection of T cells against CD4-mediated deletion lasts for several hours but ceases before the T cells become blasts.

L10 ANSWER 23 OF 38 CAPLUS COPYRIGHT 2003 ACS DUPLICATE 18
ACCESSION NUMBER: 1994:131792 CAPLUS
DOCUMENT NUMBER: 120:131792
TITLE: Effect of anti-CD4 on CD4 subsets. I. Anti-CD4 preferentially deletes resting, naive CD4 cells and spares activated CD4 cells
AUTHOR(S): Chace, Jacqueline H.; Cowdery, John S.; Field, Elizabeth H.
CORPORATE SOURCE: Coll. Med., Univ. Iowa, Iowa City, IA, 52242, USA
SOURCE: Journal of Immunology (**1994**), 152(2), 405-12
CODEN: JOIMA3; ISSN: 0022-1767
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Anti-CD4 has been extensively studied in murine models of autoimmunity and transplantation. The timing of anti-**CD4 administration** in these systems is crit. because anti-CD4 effectively blocks primary T-dependent responses but does not diminish ongoing or memory responses in immunized animals. These differential effects suggest that anti-CD4 suppresses a subpopulation of CD4+ cells. The authors previously obsd. in vitro that simultaneous activation through TCR-T3 rescued CD4+ cells from anti-CD4 elimination. From this the authors hypothesized that activated CD4+ cells resisted the effects of anti-CD4. The authors now show that in vivo treatment with anti-CD4 preferentially eliminated resting, naive CD4+ cells rather than memory and effector CD4+ cells. The CD4+ cells that remained after anti-CD4 treatment exhibited evidence of recent activation, because a higher percentage expressed IL-2R, regardless of subset phenotype. Moreover, Mls-1-primed, anti-CD4-treated mice showed a higher percentage of V.beta.6+ (Mls-1 reactive) CD4+ cells than either unprimed mice, anti-CD4-treated mice, or Mls-1-primed controls, implicating the

importance of recent activation. These anti-CD4-resistant cells also retained their functional abilities. T cells from BALB/c mice treated with anti-CD4 after Mls-1 immunization maintained their MLR proliferation against DBA/2 stimulator cells. In addn., anti-CD4 did not reduce T-dependent antibody responses in mice previously primed against the Ag cholera toxin or SRBC. Thus, activated CD4+ cells resist the suppressive effects of anti-CD4. The authors' findings have crit. implications for the ongoing clin. trials using anti-CD4.

L10 ANSWER 24 OF 38 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.DUPLICATE 19
ACCESSION NUMBER: 93347358 EMBASE
DOCUMENT NUMBER: 1993347358
TITLE: Continuous presence of CD4-PE40 is required for antiviral activity against single-passage HIV isolates and infected peripheral blood mononuclear cells.
AUTHOR: Winters M.A.; Merigan T.C.
CORPORATE SOURCE: Center for AIDS Research, Stanford University Medical Center,Stanford, CA 94305-5107, United States
SOURCE: AIDS Research and Human Retroviruses, (**1993**) 9/11 (1091-1096).
ISSN: 0889-2229 CODEN: ARHRE7
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 004 Microbiology
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
AB CD4-PE40, a recombinant protein consisting of a portion of human CD4 linked to Pseudomonas aeruginosa exotoxin, was studied in vitro to assess its ability to inhibit the replication of primary isolates of HIV. CD4-PE40 was added to cultures of phytohemagglutin (PHA)-stimulated normal peripheral blood mononuclear cells (PBMCs) infected either with the laboratory strain HIV(IIIb) or single-passage virus stocks derived from patient PBMCs. Results showed that the replication of HIV(IIIb) was inhibited by a single pulse of CD4-PE40 and, more significantly, by continuous exposure to the drug. The replication of primary virus isolates, however, was inhibited only by continuous exposure to CD4-PE40. Cultures of freshly isolated PBMCs from HIV- seropositive individuals that were directly treated with CD4-PE40 before culture also required the continuous presence of drug to demonstrate inhibition of HIV replication. These results suggest that continuous **administration** of **CD4**-PE40 may be required to produce a significant anti-HIV effect in vivo.

L10 ANSWER 25 OF 38 CAPLUS COPYRIGHT 2003 ACS DUPLICATE 20
ACCESSION NUMBER: 1993:122723 CAPLUS
DOCUMENT NUMBER: 118:122723
TITLE: IL-2 reduces graft-versus-host disease and preserves a graft-versus-leukemia effect by selectively inhibiting CD4+ T cell activity
AUTHOR(S): Sykes, Megan; Abraham, V. Simon; Harty, Mark W.; Pearson, Denise A.
CORPORATE SOURCE: Transplant. Res. Biol. Cent., Massachusetts Gen. Hosp., Boston, MA, 02129, USA
SOURCE: Journal of Immunology (**1993**), 150(1), 197-205
CODEN: JOIMA3; ISSN: 0022-1767
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The authors have recently demonstrated, in a fully MHC-mismatched murine bone marrow transplantation model, that administration of a short course of high dose IL-2 markedly diminishes graft-vs-host disease (GVHD) without compromising alloengraftment or the graft-vs-leukemia (GVL) effect of allogeneic T cells. Here was evaluated the mechanism of the dissocn. of

GVL and GVHD obsd. in this model. It was demonstrated that CD4+ T cells were required to produce severe, acute GVHD in the fully MHC-mismatched plus minor histocompatibility Ag-mismatched A/J.fwdarw.B10 strain combination. The GVHD-producing activity of A/J CD4+ T cells administered without CD8+ T cells was inhibited by IL-2 treatment. In contrast, CD8+ T cells alone mediated the GVL effect obsd. in the EL4 leukemia/lymphoma model, and CD4+ cells did not contribute to this effect. This CD8-mediated GVL activity was not inhibited by IL-2 treatment. Because naive A/J CD8+ T cells **administered** without **CD4**+ T cells did not produce acute GVHD, it was not possible to evaluate the effect of IL-2 in this model. However, when A/J donors were presensitized with B10 skin grafts, CD4-depleted A/J spleen cells were capable of causing acute GVHD in B10 recipients. This CD8-mediated GVHD was not inhibited by treatment with IL-2. However, IL-2 did partially inhibit the GVHD produced by nondepleted presensitized A/J spleen cells, probably due to selective inhibition of the function of presensitized A/J CD4+ T cells. The dissocn. of GVHD and GVL against the EL4 leukemia/lymphoma in IL-2-treated mice can therefore be explained by selective inhibition by IL-2 of CD4 activity.

L10 ANSWER 26 OF 38 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.DUPLICATE 21
ACCESSION NUMBER: 92305112 EMBASE
DOCUMENT NUMBER: 1992305112
TITLE: Phase I study of continuous-infusion soluble CD4 as a single agent and in combination with oral dideoxyinosine therapy in children with symptomatic human immunodeficiency virus infection.
AUTHOR: Husson R.N.; Chung Y.; Mordenti J.; Butler K.M.; Chen S.; Duliege A.-M.; Brouwers P.; Jarosinski P.; Mueller B.U.; Ammann A.; Pizzo P.A.
CORPORATE SOURCE: Pediatric Branch, National Cancer Institute, 9000 Rockville Pike,Bethesda, MD 20892, United States
SOURCE: Journal of Pediatrics, (**1992**) 121/4 (627-633).
ISSN: 0022-3476 CODEN: JOPDAB
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 007 Pediatrics and Pediatric Surgery
026 Immunology, Serology and Transplantation
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
AB To determine the safety and pharmacokinetics of recombinant soluble **CD4** (sCD4) **administered** by continuous intravenous infusion to children with symptomatic human immunodeficiency virus type 1 infection, we conducted a phase 1 study at the National Cancer Institute. Three dose levels of sCD4 were evaluated: 100, 300, and 1,000 .mu.g/kg per day. After an initial 12 weeks of treatment with sCD4 alone, dideoxyinosine at a dose of 90 mg/m2 every 8 hours was added and subjects were observed for an additional 12 weeks. Combination therapy was continued in patients in whom it was well tolerated. In addition to toxicity and pharmacokinetic monitoring, surrogate markers of antiviral activity were evaluated. Eleven children were enrolled in the study. During the 12 weeks of treatment with sCD4 alone, and during subsequent sCD4 plus dideoxyinosine combination therapy, no significant toxic reaction attributable to sCD4 or dideoxyinosine was encountered. Low-level anti-CD4 antibodies developed in two patients. Steady-state sCD4 levels increased proportionately at higher doses. The CD4 cell counts and serum p24 antigen levels did not provide evidence of antiviral activity. We conclude that sCD4 was well tolerated at doses up to 1,000 .mu.g/kg per day when administered by continuous intravenous infusion; however, evidence of in vivo antiviral activity was not observed in this study.

L10 ANSWER 27 OF 38 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1993:4887 BIOSIS

DOCUMENT NUMBER: PREV199395004887
TITLE: Anti-CD4 monoclonal antibody therapy in severe psoriasis.
AUTHOR(S): Morel, Patricia; Revillard, Jean-Pierre (1); Nicolas, Jean-Francois; Wijdenses, John; Rizova, Helena; Thivolet, Jean
CORPORATE SOURCE: (1) Immunology Lab., INSERM U80, Pavillon P, Hopital E. Herriot, 69437 Lyon, Cedex 03 France
SOURCE: Journal of Autoimmunity, (1992) Vol. 5, No. 4, pp. 465-477. ISSN: 0896-8411.
DOCUMENT TYPE: Article
LANGUAGE: English

AB We report here the treatment of psoriasis, a chronic inflammatory skin disease characterized by uncontrolled keratinocyte proliferation, with BB14, a CD4 murine IgG1 antibody. Three patients with severe psoriasis were treated with anti-CD4 mAb infusions (0.2 mg/kg/day for the first patient, 0.4 mg/kg/day for 2 days and 0.8 mg/kg/day during the following days for the 2 others) for 7 or 8 days, without other therapy. Rapid clinical improvement, with major reduction of the Psoriasis Area Severity Index, was observed during 1 month after treatment. Moderate decreases in CD4+ blood cells occurred in the last two patients but not in the first one. Circulating T cells coated with anti-CD4 mAb were detectable during the first 48 h in the first patient and from day 1/2 to day 7/8 in the two others. The density of CD4 molecules on the surfaces of peripheral blood lymphocytes was decreased in all patients and remained low as long as anti-CD4 mAb was detectable in patient serum. The maximal 24 h residual mAb levels ranged from 0.3 mu-g/ml in the first patient to 3.8 and 7.0 mu-g/ml in the two others. The three patients produced IgM antibodies against the anti-CD4 mAb at day 7/8 or 15 and two patients had IgG antibodies at day 15. Lesional skin samples demonstrated (1) gradual improvement in parakeratosis, papillomatosis and acanthosis, (2) decreased expression of ICAM-1 and HLA-DR by keratinocytes, (3) an increase in CD1a+ Langerhans cell number, (4) partial decrease in epidermal T cell infiltrate and (5) no major change in the dermal infiltrate composed of CD3+, TcR-alpha-beta+, CD45Ro+, HLA-DR+ T cells. We conclude that anti-**CD4** mAb **administration** can induce a rapid and major improvement in psoriatic lesions, with immunohistochemical changes different from those induced by cyclosporin A or 8-methoxypsoralen plus long wave UV light (PUVA) therapy. Our data provide strong evidence for a critical role of CD4+ lymphocytes in psoriasis.

L10 ANSWER 28 OF 38 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.DUPLICATE 22
ACCESSION NUMBER: 92263313 EMBASE
DOCUMENT NUMBER: 1992263313
TITLE: Down-regulation of lymphocyte CD4 antigen expression by administration of anti-CD4 monoclonal antibody.
AUTHOR: Morel P.; Nicolas J.F.; Wijdenes J.; Revillard J.P.
CORPORATE SOURCE: Immunology Laboratory, INSERM U80, CNRS URA 1177,Lyon, France
SOURCE: Clinical Immunology and Immunopathology, (**1992**) 64/3 (248-253). ISSN: 0090-1229 CODEN: CLIIAT
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 013 Dermatology and Venereology
026 Immunology, Serology and Transplantation
031 Arthritis and Rheumatism
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Modulation of surface CD4 antigen expression was assessed by flow cytometry after calibration with 125I-labeled anti-CD4 monoclonal antibodies (mAbs). Three patients with severe psoriasis treated with BB14 (anti-CD4 mouse IgG1) and five patients with rheumatoid arthritis treated with BL4 (anti-CD4 mouse IgG2a) were analyzed for sequential changes in surface CD4 expression on CD4+ blood lymphocytes. Anti-CD4 mAb treatment

induced a decrease of 50 to 80% of CD4 expression, with slow and partial recovery after cessation of mAb **administration**. **CD4** modulation was related to mAb dosage and mAb concentration in plasma. It was achieved at nonsaturating concentration. In vitro incubation of blood mononuclear cells induced CD4 modulation of similar kinetics and magnitude, associated with decrease of 5- 10% of CD3 expression. CD4 modulation required both an intact Fc part of the antibody and the presence of monocytes. The possible role of CD4 modulation should be considered along with other functional activities of anti-CD4 mAbs in analyzing the mechanisms of the clinical effects of these antibodies.

L10 ANSWER 29 OF 38 CAPLUS COPYRIGHT 2003 ACS DUPLICATE 23
ACCESSION NUMBER: 1993:145871 CAPLUS
DOCUMENT NUMBER: 118:145871
TITLE: CD4 immunoadhesins in anti-HIV therapy: new developments
AUTHOR(S): Chamow, Steven M.; Duliege, Anne Marie; Ammann, Art; Kahn, James O.; Allen, J. Davis; Eichberg, Jorg W.; Byrn, Randal A.; Capon, Daniel J.; Ward, Rebecca H. R.; Ashkenazi, Avi
CORPORATE SOURCE: Genentech, Inc., South San Francisco, CA, 94080, USA
SOURCE: International Journal of Cancer, Supplement (**1992**), 7(Bispecific Antibodies Targeted Cell Cytotoxic), 69-72
CODEN: IJSUEZ; ISSN: 0898-6924
DOCUMENT TYPE: Journal
LANGUAGE: English
AB CD4, the cell-surface receptor for the human immunodeficiency virus (HIV), is a member of the Ig gene superfamily. It contains 4 extracellular sequences homologous to Ig variable domains, the first of which (V1) is sufficient for binding to HIV. To develop CD4 as an anti-HIV therapeutic, a CD4 immunoadhesin (CD4-IgG), a fusion protein was engineered contg. the V1 and V2 domains of CD4 with the hinge and Fc regions of human Ig heavy chain. A chimeric protein of this type has several advantages compared to the sol. receptor, including a greatly extended in vivo half-life and greater avidity for HIV; moreover, like an antibody, it performs effector functions via its Fc domains, such as complement activation and antibody-dependent cell-mediated cytotoxicity. In vivo expts. show that CD4-IgG protects against HIV-I IIIB infection of chimpanzees when administered prior to viral challenge. In addn., CD4-IgG is transferred efficiently across the placenta from mother to fetus in rhesus monkeys. To evaluate its safety in humans, a phase-I clin. trial was conducted in adult patients with AIDS and AIDS-related complex. In a total of 16 patients, **administration** of **CD4**-IgG was well tolerated at doses up to 1000 .mu.g/kg of body wt., with no important clin. or immunol. toxicities noted.

L10 ANSWER 30 OF 38 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.DUPLICATE 24
ACCESSION NUMBER: 92209324 EMBASE
DOCUMENT NUMBER: 1992209324
TITLE: Effects of dexamethasone on selective lymphocyte subpopulations in hypercortisolemic patients with anorexia nervosa and with bulimia nervosa: Preliminary report.
AUTHOR: Chiappelli F.; Gwirtsman H.E.; Gormley G.J.; Lowy M.T.; Esmail I.; Nguyen - L.D.; Nguyen L.; Strober M.; Weiner H.
CORPORATE SOURCE: Division of Biological Psychiatry, Department of Psychiatry, Harbor-UCLA, 1000 W. Carson Street,Torrance, CA 90509-1768, United States
SOURCE: International Journal of Eating Disorders, (**1992**) 12/1 (37-46).
ISSN: 0276-3478 CODEN: INDIDJ
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 003 Endocrinology
026 Immunology, Serology and Transplantation

032 Psychiatry
037 Drug Literature Index

LANGUAGE: English
SUMMARY LANGUAGE: English

AB The studies reported here describe the effects of intravenous (IV) administration of the synthetic glucocorticoid dexamethasone (DEX) on certain neuroendocrine and immunological measures in hypercortisolemic patients with anorexia nervosa (AN) and with bulimia nervosa (BN). The results demonstrate that failure to suppress cortisol levels after DEX administration in patients with AN is associated with failure to reduce the level of adrenocorticotropic hormone (ACTH), the ratio of CD4-to-CD8 lymphocytes, the percent and number of circulating CD4 lymphocytes, and the percent and number of virgin CD4 cells (**CD4**+CD45RA+). **Administration** of DEX to patients with BN suppressed plasma ACTH and cortisol levels, reduced the CD4/CD8 ratio and the percent and number of CD4 and of CD4+CD45RA+ lymphocytes, and increased the percent and number of circulating CD8 lymphocytes. Administration of DEX failed to alter other immune measures in either patient population, including circulating populations of B and natural killer cells, the proliferative response to T-cell mitogen, and the number of glucocorticoid receptors in circulating lymphocytes.

L10 ANSWER 31 OF 38 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 91137730 EMBASE
DOCUMENT NUMBER: 1991137730
TITLE: Immunomodulation by monoclonal antibodies directed against cell adhesion molecules: A special case for CD4 monoclonal antibodies.
AUTHOR: Riethmuller G.; Reiter C.; Kakavand B.; Schattenkirchner M.; Kruger K.; Eisenburg J.; Rieber E.P.
CORPORATE SOURCE: Institute of Immunology, University of Munich, Munich, Germany
SOURCE: European Journal of Rheumatology and Inflammation, (**1991**) 11/1 (177-181).
ISSN: 0140-1610 CODEN: EJRIDH
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Conference Article
FILE SEGMENT: 031 Arthritis and Rheumatism
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English

AB The induction as well as the effector phase of cellular immune reactions depend on specific cell-cell contacts. Besides the specific antigen receptors, adhesion molecules on the cell surface play a pivotal role in the guidance and stabilisation of temporary contacts required for inter- and intracellular signal transduction. Of the various adhesion molecules, such as ICAM-1, CD2, LFA-1 and LFA-3, the CD4 and CD8 glycoproteins play a particular role because they direct T-cell subsets specifically to either major histocompatibility complex (MHC) class II or MHC class I molecules which are associated with the triggering antigen on antigen-presenting cells. The blockade of both adhesion molecules by antibodies efficiently inhibits the function of the respective T-cell subsets. One of the most efficient ways to suppress T-cells in experimental autoimmune disorders has been the therapeutic **administration** of **CD4** monoclonal antibodies. Studies have therefore concentrated on the immunomodulation induced by CD4 monoclonal antibodies in patients with rejection crises of organ transplants and patients with rheumatoid arthritis.

L10 ANSWER 32 OF 38 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1991:400766 CAPLUS
DOCUMENT NUMBER: 115:766
TITLE: Kit and composition useful for treatment or prevention of human immunodeficiency virus 1 (HIV-1) infections

INVENTOR(S): Volvovitz, Franklin
PATENT ASSIGNEE(S): Microgenesys, Inc., USA
SOURCE: Eur. Pat. Appl., 4 pp.
CODEN: EPXXDW

DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 385909	A2	19900905	EP 1990-610014	19900301 <--
EP 385909	A3	19910410		
EP 385909	B1	19940713		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE				
CA 2011299	AA	19900903	CA 1990-2011299	19900301 <--
AU 9050610	A1	19901101	AU 1990-50610	19900302 <--
AU 635001	B2	19930311		
JP 03163027	A2	19910715	JP 1990-52581	19900302 <--

PRIORITY APPLN. INFO.: US 1989-318272 19890303

AB The title kit or compn. comprises immunogenic protein of HIV-1 and/or CD4 antigen and/or its derivs. Preferably **CD4** is **administered** first, followed by the immunogenic protein (no data).

L10 ANSWER 33 OF 38 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.DUPLICATE 25
ACCESSION NUMBER: 90349286 EMBASE
DOCUMENT NUMBER: 1990349286
TITLE: Graft-versus-host mortality induced by noncytolytic CD4+ T cell clones specific for non-H-2 antigens.
AUTHOR: Miconnet I.; Huchet R.; Bonardelle D.; Motta R.; Canon C.; Garay-Rojas E.; Kress M.; Reynes M.; Halle-Pannenko O.; Bruley-Rosset M.
CORPORATE SOURCE: INSERM U.267, Hopital Paul Brousse, 14 Avenue Paul-Vaillant-Couturier, 94800 Villejuif, France
SOURCE: Journal of Immunology, (**1990**) 145/7 (2123-2131).
ISSN: 0022-1767 CODEN: JOIMA3
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 005 General Pathology and Pathological Anatomy
022 Human Genetics
025 Hematology
026 Immunology, Serology and Transplantation
LANGUAGE: English
SUMMARY LANGUAGE: English

AB The relative contribution of individual non-H-2 Ag and of T cell subsets that initiate graft-vs-host reaction (GVHR) as well as the mechanism responsible for histopathologic lesions are still a matter of debate. To address these questions and to favor the selection of T cells primed in vivo against non-H-2 Ag important in GVHR we derived T cell clones from spleens of (DBA/2 x B10.D2)F1 (H-2(d)) mice developing this reaction after the graft of B10.D2 (H-2(d)) cells incompatible for numerous non-H-2 Ag plus Mlsa. The pattern of reactivity of eight selected clones against cells from different strains of mice including (BXD)RI strains indicated that one CD4+ clone is specific for Mlsa and seven additional clones (six CD4+ and one CD8+) are specific for four different non-H-2 Ag (Ag.I-IV) and proliferate in an H-2-restricted manner. The same series of experiments suggested that Ag.I and II are poorly polymorphic and allowed to propose the localisation of the genes controlling Ag.I (chromosome 1) and Ag.III (chromosome 4). All the clones show a triple (.alpha., .beta., .gamma.) mRNA transcript for TCR but at their surface they express the .alpha./.beta.-heterodimer. The clone specific for Mlsa expresses V.beta.6 and that specific for Ag.IV expresses V.beta.8.1. Rapid mortality accompanied by clinical and histologic signs of severe GVHR was observed after **administration** of **CD4**+ clones (together with host-syngeneic bone marrow) derived early after grafting and specific for

Ag.I and II but not after administration of: 1) CD8+ cytolytic clone derived early after grafting and specific for Ag.IV; 2) CD4+ clones derived late after grafting and specific for Ag.III; and 3) CD4+ clone specific for M1sa. A specific for M1sa. a clear correlation was established between the capacity of CD4+ clones to induce GVHR mortality, to mediate host-specific DTH and to release a high level of TNF. In conclusion: 1) the reaction against a single non-H-2 Ag is sufficient to provoke lethal GVHR; 2) the capacity to provoke GVHR mortality depends on antigenic specificity and functional properties of the responding clones; 3) the inflammatory process mediated by CD4+ clones may play a major role whereas the specific CD8+ T cell-mediated cytolytic activity is not necessarily lethal.

L10 ANSWER 34 OF 38 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1991:526428 CAPLUS
DOCUMENT NUMBER: 115:126428
TITLE: Peptides derived from the CDR3-homologous domain of the CD4 molecule are specific inhibitors of HIV-1 and SIV infection, virus-induced cell fusion, and postinfection viral transmission in vitro: implications for the design of small-peptide anti-HIV therapeutic agents
AUTHOR(S): Rausch, D. M.; Hwang, K. M.; Padgett, M.; Voltz, A. H.; Rivas, A.; Engleman, E.; Gaston, I.; McGrath, M.; Fraser, B.; et al.
CORPORATE SOURCE: Lab. Cell Biol., Natl. Inst. Ment. Health, Bethesda, MD, 20892, USA
SOURCE: Annals of the New York Academy of Sciences (**1990**), 616(AIDS: Anti-HIV Agents, Ther., Vaccines), 125-48
CODEN: ANYAA9; ISSN: 0077-8923
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The toxicity, pharmacokinetics and effects of immune parameters of a prototype **CD4** peptide **administered** during SIV infection of rhesus macaques, antiviral potency, and mechanism of action f several prototype CD4 peptides are described.

L10 ANSWER 35 OF 38 CAPLUS COPYRIGHT 2003 ACS DUPLICATE 26
ACCESSION NUMBER: 1989:210685 CAPLUS
DOCUMENT NUMBER: 110:210685
TITLE: Effect of CD4 monoclonal antibody in vivo on lesion development, delayed-type hypersensitivity and interleukin 3 production in experimental murine cutaneous leishmaniasis
AUTHOR(S): Liew, F. Y.; Millott, S.; Lelchuk, R.; Cobbold, S.; Waldmann, H.
CORPORATE SOURCE: Dep. Exp. Immunobiol., Wellcome Res. Lab., Beckenham/Kent, BR3 3BS, UK
SOURCE: Clinical and Experimental Immunology (**1989**), 75(3), 438-43
CODEN: CEXIAL; ISSN: 0009-9104
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Highly susceptible BALB/c mice subjected to adult thymectomy followed by prolonged (15 wk), twice-weekly injections of a low dose (100 .mu.g) of CD4 monoclonal antibody (MoAb) develop resistance to otherwise uniformly fatal and disseminating Leishmania major infection. Similar treatment after the lesion establishment also has no effect. **CD4** MoAb **administered** after the lesion establishment also has no effect. Mice which become resistant following CD4 MoAb treatment developed the classical delayed-type hypersensitivity (DTH) which persisted at 72 h after footpad injection with killed L. major promastigotes. A substantial degree of resistance can also be induced in the BALB/c mice with two i.v. high doses of 500 .mu.g of CD4 MoAb given immediately prior to L. major

infection. The treated mice developed classical DTH and smaller lesions. The spleen cells from these mice also produced lower levels of IL-3 compared to that of untreated control mice when cultured with L. major antigens in vitro. Genetically resistant CBA mice treated with CD4 MoAb developed larger lesions but lower levels of classical DTH compared to untreated mice. These data confirm and extend earlier reports on the prophylactic effect of CD4 MoAb in susceptible BALB/c mice and the disease exacerbative effect in the resistant CBA mice.

L10 ANSWER 36 OF 38 CAPLUS COPYRIGHT 2003 ACS DUPLICATE 27
ACCESSION NUMBER: 1989:73646 CAPLUS
DOCUMENT NUMBER: 110:73646
TITLE: T help requirements for the generation of an in vivo IgE response: a late acting form of T cell help other than IL-4 is required for IgE but not for IgG1 production
AUTHOR(S): Finkelman, Fred D.; Holmes, Joanne; Urban, Joseph F., Jr.; Paul, William E.; Katona, Ildy M.
CORPORATE SOURCE: Dep. Med., Univ. Health Sci., Bethesda, MD, 20814, USA
SOURCE: Journal of Immunology (**1989**), 142(2), 403-8
CODEN: JOIMA3; ISSN: 0022-1767
DOCUMENT TYPE: Journal
LANGUAGE: English
AB To further define requirements for T cell help in the stimulation of an in vivo IgE response, a system was studied in which the injection of mice with a goat antibody to mouse IgD (GaMD) stimulates large polyclonal IgG1 and IgE responses. In this system, both responses are blocked by anti-CD4 antibody, but only the IgE response is blocked by anti-interleukin 4 [(anti-IL-4)] antibody. Anti-CD4 antibody, if injected 5 days after GaMD, inhibited the GaMD-induced IgE response to a much greater extent than the IgG1 response, even though both responses occur simultaneously and are inhibited to an equal extent by optimal or suboptimal doses of anti-**CD4** antibody **administered** 2 days after GaMD. Even a suboptimal, 50-.mu.g dose of anti-CD4 antibody, when injected 5 days after GaMD, inhibited the IgE response to a much greater extent than did an optimal 10-mg dose of anti-IL-4 antibody injected at the same time, even though 10 mg of anti-IL-4 antibody more completely inhibited GaMD-induced IgE prodn. than did 50 .mu.g of anti-CD4 antibody when injected 2 days after GaMD. Thus, a late acting form of T cell help other than IL-4 is important for the generation of an IgE response but not an IgG1 response in GaMD-immunized mice.

L10 ANSWER 37 OF 38 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 90074158 EMBASE
DOCUMENT NUMBER: 1990074158
TITLE: Perturbation of T-cell differentiation in lethally irradiated rats reconstituted with syngeneic bone marrow and treated with Cyclosporin-A.
AUTHOR: Bos G.M.J.; Majoor G.D.; Van Breda Vriesman P.J.C.
CORPORATE SOURCE: Department of Immunology, University of Limburg, P.O.B. 616, 6200 MD Maastricht, Netherlands
SOURCE: Thymus, (**1989**) 14/1-3 (155-161).
ISSN: 0165-6090 CODEN: THYMDB
COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Conference Article
FILE SEGMENT: 005 General Pathology and Pathological Anatomy
014 Radiology
025 Hematology
026 Immunology, Serology and Transplantation
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Lethally irradiated rats reconstituted with syngeneic bone marrow and treated for 40 or 80 days with Cyclosporin A (Cy-A) contract disease mimicking graft-versus-host disease about 3 weeks after withdrawal of the

drug. We investigated the reconstitution of peripheral blood lymphocytes after this treatment. A selective effect on the regeneration of the CD4- cells was observed. During Cy-A **administration CD4** +-cell regeneration was almost completely suppressed, but within 3 weeks after withdrawal of the drug such cells reappeared in blood and reached pre-irradiation levels about 6 weeks later. The coincidence of the reappearance of CD4+ cells and the onset of autoimmune disease suggests a causal relation between both events.

L10 ANSWER 38 OF 38 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 89263139 EMBASE
DOCUMENT NUMBER: 1989263139
TITLE: Recurrence of insulitis in the NOD mouse after early prolonged anti-CD4 monoclonal antibody treatment.
AUTHOR: Charlton B.; Mandel T.E.
CORPORATE SOURCE: Walter and Eliza Hall Institute of Medical Research, Royal Melbourne Hospital, Parkville, Vic. 3050, Australia
SOURCE: Autoimmunity, (**1989**) 4/1-2 (1-7).
ISSN: 0891-6934 CODEN: AUIMEI
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal
FILE SEGMENT: 026 Immunology, Serology and Transplantation
037 Drug Literature Index
003 Endocrinology
LANGUAGE: English
SUMMARY LANGUAGE: English
AB The treatment of young NOD mice with continuous anti-**CD4** mAb **administration** has previously been shown to prevent insulitis from developing. It has also been shown that insulitis, once present, can be abolished by anti-CD4 mAb treatment, but that the insulitis recurs after treatment stops. We have studied the effect of treating young NOD/Wehi mice with a limited course of anti-CD4 mAb to determine if any long term prevention of insulitis ensued. Anti-CD4 mAb (H129.19) was given i.p. weekly to 10 female NOD/Wehi mice from 25-100 days of age. Control mice received no treatment. The pancreas of the mice were examined histologically at 100 and 180 days of age and severity of insulitis graded from 0-100%. The insulitis grade in treated mice at 100 days was 5 .+-. 2% compared with 29 .+-. 26% in age matched control mice ($p < 0.01$). At 180 days of age the insulitis grade in treated mice was 29 .+-. 23% compared with 47 .+-. 22% in age matched controls (NS). Thus insulitis was prevented from developing by early treatment with anti-CD4 mAb but developed later when treatment was stopped. Early anti-CD4 mAb treatment with anti-CD4 mAb but developed later when treatment was stopped. Early anti-CD4 mAb treatment does not therefore appear to produce a tolerant state so averting insulitis development and, insulitis can still develop in older NOD mice.

```
=>
=> s (UCP) (P) (B7 (1N) 2) (P) (CD)
L11           0 (UCP) (P) (B7 (1N) 2) (P) (CD)

=> s (UCP) (P) (B7 (1N) 2) (P) (CD4)
L12           0 (UCP) (P) (B7 (1N) 2) (P) (CD4)

=> s (UCP) and (B7 (1N) 2) and (CD4)
L13           0 (UCP) AND (B7 (1N) 2) AND (CD4)

=> s administ? (1N) ( antibod? (5N) (Class (1N) II))
L14           5 ADMINIST? (1N) (ANTIBOD? (5N) (CLASS (1N) II))

=> dup rem l14
PROCESSING COMPLETED FOR L14
L15           2 DUP REM L14 (3 DUPLICATES REMOVED)
```

=> dis l15 ibib abs

L15 ANSWER 1 OF 2 MEDLINE DUPLICATE 1
ACCESSION NUMBER: 93007993 MEDLINE
DOCUMENT NUMBER: 93007993 PubMed ID: 1394221
TITLE: A murine model for antibody-directed targeting of vascular endothelial cells in solid tumors.
AUTHOR: Burrows F J; Watanabe Y; Thorpe P E
CORPORATE SOURCE: University of Texas Southwestern Medical Center, Department of Pharmacology, Dallas 75230.
CONTRACT NUMBER: 1RO1CA 54168-02 (NCI)
SOURCE: CANCER RESEARCH, (1992 Nov 1) 52 (21) 5954-62.
Journal code: 2984705R. ISSN: 0008-5472.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199211
ENTRY DATE: Entered STN: 19930122
Last Updated on STN: 19930122
Entered Medline: 19921118

AB An attractive approach to the therapy of solid tumors would be to target cytotoxic agents or coagulants to the vasculature of the tumor rather than to the tumor cells themselves. This strategy has 3 advantages: (a) it should be applicable to many types of solid tumors because all require a blood supply for survival and growth; (b) the target endothelial cells are directly accessible through the blood and are normal cells, making the outgrowth of resistant mutants unlikely; and (c) there is an in-built amplification mechanism because thousands of tumor cells are reliant on each capillary for nutrients and oxygen. Despite its theoretical attractions, the approach of tumor vascular targeting has not been testable because antibodies that recognize tumor vascular endothelial cell antigens with adequate specificity are currently not available. In this study, we developed a model system in which to investigate the antibody-directed targeting of vascular endothelial cells in solid tumors in mice. A neuroblastoma transfected with the mouse interferon-gamma gene, C1300(Mu gamma), was grown in antibiotic-treated BALB/c nude mice. The interferon-gamma secreted by the tumor induces the expression of major histocompatibility complex Class II antigens on the tumor vascular endothelium. Class II antigens are absent from the vasculature of normal tissues, although they are present on B-lymphocytes, cells of monocyte/macrophage lineage, and some epithelial cells. Anti-**Class II antibody administered** i.v. strongly stains the tumor vasculature, whereas an antitumor antibody directed against a major histocompatibility complex Class I antigen of the tumor allograft produces classical perivascular tumor cell staining. This model should enable the theoretical superiority of tumor vascular targeting over conventional tumor cell targeting to be tested.

=> dis l15 ibib abs 2

L15 ANSWER 2 OF 2 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 84162142 EMBASE
DOCUMENT NUMBER: 1984162142
TITLE: Occasional review - HLA and leprosy: A re-evaluation.
AUTHOR: Van Eden W.; De Vries R.R.P.
CORPORATE SOURCE: Department of Immunohaematology and Bloodbank, University Hospital Leiden, 2333 AA Leiden, Netherlands
SOURCE: Leprosy Review, (1984) 55/2 (89-104).
CODEN: LEREAA
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal
FILE SEGMENT: 051 Leprosy and other Mycobacterial Diseases
013 Dermatology and Venereology

026 Immunology, Serology and Transplantation

LANGUAGE: English

AB The recent findings described in the present paper provide a number of starting points for further in-depth investigation. With respect to practical implications for leprosy control, but also with respect to the understanding of, presumably, some essentials of the genetic control of the immune response in man, the HLA-linked control of the susceptibility to lepromatous leprosy deserves special attention. For obvious reasons, attempts should be made to test the hypothesis of leprosy-specific Is genes. One approach could be to present leprosy antigens to T-cells from lepromatous leprosy patients by allogeneic antigen presenting cells which share only one haplotype or one DR specificity with the T-cell. In this way, responses restricted by the responder haplotype or molecules could be obtained circumventing the involvement of Is gene products. Alternatively, attempts may be made to block the Is gene products, as was shown successfully in non-responder mice for the LDH-B antigen, with the use of antibodies, preferably monoclonal, recognizing distinct epitopes on class II molecules. That the latter approach could have an impact on future prevention or immuno-therapy was indicated by mouse experiments showing that the **administration** of **antibodies** directed against certain **class II** H-2 products could prevent or modulate immunopathological disease processes. Speculating along these lines one could think of adding antibodies directed against leprosy Is gene products, possibly MT1, as non-conventional 'adjuvants' to vaccines used for prevention or immuno-therapy. By blocking the effect of the presumed leprosy-specific Is gene products, one might be able to convert specific non-responders into responders. A promising beneficial therapeutic effect of multiple inoculations with a mixture of M. leprae and BCG has been shown in some but not all BL and LL patients. The addition of the proper blocking antibodies to such a 'vaccine' could thus be one of the possibilities to raise the effectiveness of this kind of immunotherapy. To improve our understanding of the HLA-associated control in leprosy, better tools for investigation are expected to become available, namely antigen-specific T-cell lines grown from leprosy patients (and healthy controls). These can be studied for HLA-class II restriction properties for leprosy antigens presented by selected allogeneic antigen presenting cells obtained from both healthy individuals and leprosy patients.

=> end
ALL L# QUERIES AND ANSWER SETS ARE DELETED AT LOGOFF
LOGOFF? (Y)/N/HOLD:y

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	236.28	236.49
DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE ENTRY	TOTAL SESSION
CA SUBSCRIBER PRICE	-16.93	-16.93

STN INTERNATIONAL LOGOFF AT 16:21:28 ON 23 MAR 2003